



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 39

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 39

Editorial Advisory Board

R. A. Abramovitch, *Clemson, South Carolina*

A. Albert, *Canberra, Australia*

A. T. Balaban, *Bucharest, Romania*

A. J. Boulton, *Norwich, England*

H. Dorn, *Berlin, G.D.R.*

S. Gronowitz, *Lund, Sweden*

T. Kametani, *Tokyo, Japan*

O. Meth-Cohn, *South Africa*

C. W. Rees, FRS, *London, England*

E. C. Taylor, *Princeton, New Jersey*

M. Tišler, *Ljubljana, Yugoslavia*

J. A. Zoltewicz, *Gainesville, Florida*

Advances in

HETEROCYCLIC CHEMISTRY

Edited by

ALAN R. KATRITZKY, FRS

*Kenan Professor of Chemistry
Department of Chemistry
University of Florida
Gainesville, Florida*

1986



Volume 39

ACADEMIC PRESS, INC.

Harcourt Brace Jovanovich, Publishers

Orlando San Diego New York Austin Boston
London Sydney Tokyo Toronto

COPYRIGHT © 1986 BY ACADEMIC PRESS, INC.
ALL RIGHTS RESERVED.
NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR
TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC
OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR
ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT
PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC.
Orlando, Florida 32887

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
24-28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

ISBN 0-12-020639-0

PRINTED IN THE UNITED STATES OF AMERICA

86 87 88 89

9 8 7 6 5 4 3 2 1

Contents

PREFACE.....	vii
--------------	-----

The Reduction of Nitrogen Heterocycles with Complex Metal Hydrides

JAMES G. KEAY

I. Scope of Review	2
II. Introduction	3
III. Reduction of Heterocycles Containing One Nitrogen Atom	6
IV. Reductions of Heterocycles Containing Two Nitrogen Atoms	42
V. Reductions of Heterocycles Containing Three Nitrogen Atoms	56
VI. Reduction of Heterocycles Containing Four Nitrogen Atoms	60
VII. Reduction of Fused Heterocycles	61

Mass Spectrometry of Nucleic Acids

KRZYSZTOF JANKOWSKI, J. R. JOCELYN PARÉ,
AND ROBERT H. WIGHTMAN

I. Introduction	79
II. Bases	82
III. Nucleosides	85
IV. Nucleotides	91
V. Nucleic Acids and Polynucleotides	95
VI. Sequence of Ribo- and Deoxyribonucleotides and Nucleic Acids	106
VII. Concluding Remarks	112
VIII. Addendum	113

Chemistry of 8-Azapurines (1,2,3-Triazolo[4,5-*d*]pyrimidines)

ADRIEN ALBERT

I. Introduction: Nomenclature, Tautomerism, Earlier Reviews, Databank	118
II. Structure and Physical Properties	121
III. Reactivity	134
IV. Synthesis	156
V. Biological and Industrial Applications	171

Application of Aziridines to the Synthesis of Natural Products**TETSUJI KAMETANI AND TOSHIO HONDA**

I. Introduction	182
II. Synthesis of Isoquinoline Alkaloids	182
III. Syntheses of Indole Alkaloids	213
IV. Miscellaneous	222

Metallacycloalkanes and -alkenes**EKKEHARD LINDNER**

I. Introduction	238
II. Metallacycloalkanes without and with Additional Heteroatoms.	239
III. Metallacycloalkenes without and with Additional Heteroatoms.	262

**Tricyclic Compounds with a Central Pyrimidine Ring
and One Bridgehead Nitrogen****ISTVÁN HERMECZ AND LELLE VASVÁRI-DEBRECZY**

I. Introduction	282
II. Tricyclic Compounds Containing a Three-Membered Ring	284
III. Other Angular Annulated Ring Systems with Nitrogen Away from the Ring Angle (Type I)	290
IV. Other Angular Annulated Ring Systems with Nitrogen in the Ring Angle (Type II)	297
V. Other Linearly Annulated Ring Systems (Type III)	317
VI. Appendix	380
Note Added in Proof	385

CUMULATIVE INDEX OF TITLES	387
----------------------------------	-----

Preface

Volume 39 of *Advances in Heterocyclic Chemistry* encompasses six chapters. Of these, two are updates of previously treated subjects. Thus, J. G. Keay in his survey of the reductions of heterocycles by complex hydrides has updated the chapter by P. S. Anderson and R. E. Lyle which appeared in Volume 6 of this series. Some of the most recent aspects of the mass spectra of heterocycles are summarized by J. R. J. Paré and co-workers; this subject was previously treated in Volume 7.

Two groups of polycyclic heterocycles are treated: the 8-azapurines by A. Albert and tricyclic fused-pyrimidines by I. Hermecz and L. Vasvári-Debrezsy.

T. Kametani and T. Honda discuss the uses of aziridines in the synthesis of natural products, and finally E. Lindner gives an account of metallacycloalkanes that reminds us of the fact that heterocyclic compounds in which most of the transition metals can play the part of the heteroatom are now known.

ALAN R. KATRITZKY

This Page Intentionally Left Blank

The Reduction of Nitrogen Heterocycles with Complex Metal Hydrides

JAMES G. KEAY

Reilly Tar & Chemical Corporation, Indianapolis, Indiana 46204

I. Scope of Review	2
II. Introduction	3
III. Reduction of Heterocycles Containing One Nitrogen Atom	6
A. Pyridines	6
1. With Borohydride	6
2. With Aluminum Hydrides	10
3. Other Hydrides	12
B. Pyridones	12
1. With Aluminum Hydrides	12
C. Pyridinium Salts	13
1. With Borohydrides	13
2. With Aluminum Hydrides	23
D. 1-Alkoxypyridinium Salts and Pyridine 1-Oxides	24
E. Cyclic Imines	25
F. Quinolines	25
1. With Borohydrides	25
2. With Aluminum Hydrides	28
G. Quinolinium Salts	30
1. With Borohydride	30
2. With Aluminum Hydrides	32
H. Isoquinolines	32
1. With Borohydrides	32
2. With Aluminum Hydrides	33
I. Isoquinolinium Salts	33
1. With Borohydride	33
2. With Aluminum Hydrides	35
J. Indoles	35
K. 1,2-Oxazoles	38
L. 1,3-Oxazoles	40
M. 1,3-Thiazoles	40
N. 1,3-Thiazines	41
IV. Reductions of Heterocycles Containing Two Nitrogen Atoms	42
A. Pyrazoles	42
B. Imidazoles	44
C. Benzimidazoles	46
D. 1,2,4-Oxadiazoles	46

E. Pyridazines	46
F. Pyrimidines	48
G. Pyrazines	50
H. Cinnolines	51
I. Quinazolines	52
J. Quinoxalines	53
K. 1,2-Diazepines	54
L. 1,4-Diazepines	55
M. 1,5-Benzodiazepines	55
V. Reduction of Heterocycles Containing Three Nitrogen Atoms	56
A. 1,2,3-Triazoles	56
B. 1,2,4-Triazoles	56
C. Benzotriazoles	57
D. 1,2,3-Triazines	58
E. 1,2,4-Triazines	59
F. 1,3,5-Triazines	60
VI. Reduction of Heterocycles Containing Four Nitrogen Atoms	60
A. Tetrazoles	60
VII. Reduction of Fused Heterocycles	61
A. Quinolizines	61
B. Azolopyridazines	62
C. Azolopyrimidines	63
1. 1,2,5-Oxadiazolo[3,4- <i>d</i>]pyrimidine	63
2. Imidazolo[4,5- <i>d</i>]pyrimidine	63
3. Pyrazolo[1,5- <i>a</i>]pyrimidine	66
D. Thieno[2,3- <i>d</i>]pyrimidine	67
E. Thienopyridines	67
1. Thieno[3,2- <i>c</i>]- and Thieno[2,3- <i>c</i>]pyridines	67
F. Azoloazepines	68
1. Pyrazolo[3,4- <i>b</i>]-1,4-diazepine	68
G. Azanaphthalenes	68
1. Pyrido[3,2- <i>e</i>]- and Pyrido[3,4- <i>e</i>]-1,2,4-triazines	68
2. Pyrazino[2,3- <i>d</i>]pyrimidine	69
3. Pyrimidino[4,5- <i>d</i>]pyridazine	70
4. Pyrido[3,4- <i>d</i>]pyrimidine	70
5. Pyrido[2,3- <i>b</i>]pyrazine	71
6. Pyrido[2,3- <i>d</i>]pyridazine	71
7. Pyrido[4,3- <i>b</i>]pyridine	72
H. Azoloindoles	72
1. Pyrido[2,3- <i>b</i>]-, -[3,4- <i>b</i>]- and -[4,3- <i>b</i>]indoles	72
I. 1,3-Thiazolo[2,3- <i>a</i>]isoquinoline	74
J. 1,4-Thiazeno[4,5- <i>a</i>]quinoline and -[4,5- <i>a</i>]quinazoline	74
K. Benzo[<i>d,e</i>]quinazoline	75
L. Indolo[2,3- <i>a</i>]quinolizine	76
M. Pyrido[3,2,1- <i>k,l</i>]phenothiazines	76

I. Scope of Review

This article covers the literature published between the years 1965 and 1983 and that contained in *Chemical Abstracts*, Volumes 64–99 inclusive.

Pertinent 1984 literature is also included. It serves to update the review of Lyle and Anderson, which covered the earlier literature.¹

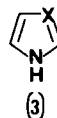
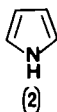
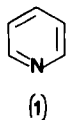
Substrates covered are listed in the index page. Most investigators have worked with the complex hydrides of boron and aluminum; therefore reactions with these form the principal part of the discussion. Some work with other organometallic hydrides and complex hydrides of some transition metals is also described.

II. Introduction

The previous review on this subject was published in 1966.¹ Though the number of reagents and systems investigated has been greatly expanded since that time, this review is structured after the Lyle and Anderson document. Some of the earlier observations regarding general reactivity principles deserve restatement.

Complex metal hydrides are nucleophilic reagents that formally add hydride to polarized carbon-carbon or carbon-heteroatom double bonds. The two best known reagents of this type are lithium aluminum hydride (LAH) and sodium borohydride (NBH). The former is moisture sensitive and generally used in ethers; the latter is milder and is most often employed in hydroxylic solvents. The efficacy and selectivity of these reagents is greatly affected by structural modifications [e.g., $\text{LiAlH}_2(\text{O}-t\text{-Bu})_2$], for instance, the addition of Lewis acids and mixed hydride formation. Solvents can also affect the power of the reducing agent; this is particularly so with sodium borohydride. Many modified complex metal hydrides are now known. A comprehensive review on complex metal hydrides was published in 1979.²

Those heterocyclic systems attacked by complex metal hydrides are required to be relatively electron deficient. Nitrogen heterocycles in which the heteroatom contributes a single electron to the π system are considered electron deficient (e.g., **1**). However, systems where the nitrogen atom contributes two electrons are considered electron rich (e.g., **2**) and are not normally attacked by metal hydrides. Aromatic species that contain both a "pyridine-like" (**1**) and a "pyrrole-like" (**2**) heteroatom (e.g., **3**) exhibit be-

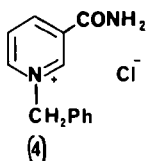


¹ P. S. Anderson and R. E. Lyle, *Adv. Heterocycl. Chem.* **6**, 45 (1966).

² A. Hajos, "Complex Hydrides and Related Reducing Agents in Organic Synthesis." Am. Elsevier, New York, 1979.

havior due to each atom and are generally capable of being attacked by these reagents.

Traditionally, the mechanism by which complex metal hydrides reduce unsaturated compounds has been viewed as nucleophilic and regarded as a direct hydride transfer from reagent to substrate.³ However, in the last few years this view has been radically challenged amid reports of the operation of single-electron transfer (SET) processes. Ashby and co-workers have shown that such mechanisms do occur in the reaction of both organometallic compounds or simple metal hydrides with a variety of substrates.^{4,5} The first suggestion that an alternative radical mechanism may operate in the borohydride reduction of pyridinium ions was put forward by Uzienko and Yasnikov in 1972 during investigation of 1-benzyl-3-carboxamidopyridinium chloride (4).⁶



Conclusive evidence for the formation of radical intermediates in the reaction of pyridine with LAH⁷ itself has not been forthcoming to date. This is due to the short lifetime of such radicals and their propensity toward coupling with hydrogen or other pyridine radicals. However, the use of substrates that generate radicals with a greater steric requirement (e.g., 1,10-phenanthroline, 2,2-bipyridine, isoquinoline) has allowed detection of radicals by ESR spectrometry. Much stronger signals were observed with the less reactive hydrides, lithium di- and lithium tri-*tert*-butoxyaluminum hydride. Much higher radical concentrations, up to 27%, were observed. Electron-spin resonance signals were still detectable one month later in some cases.⁷ In the absence of more readily attacked species, excess pyridine is known to form lithium tetra(dihydropyridinyl)aluminates with LAH.⁸

Such intermediate complexes react with heterocycles at much slower rates and allow observation of the radical intermediates. Indeed, ratios of substrate to hydride such that the available hydrogens could be involved in intermediate heterocyclic hydride complexes (e.g., 5) resulted in the highest

³ E. C. Ashby, A. B. Goel, R. N. DePriest, and H. S. Prasad, *J. Am. Chem. Soc.* **103**, 973 (1981).

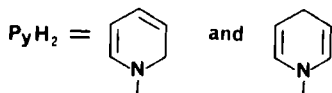
⁴ E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Am. Chem. Soc.* **102**, 7779 (1980).

⁵ E. C. Ashby and J. R. Bowers, Jr., *J. Am. Chem. Soc.* **103**, 2242 (1981).

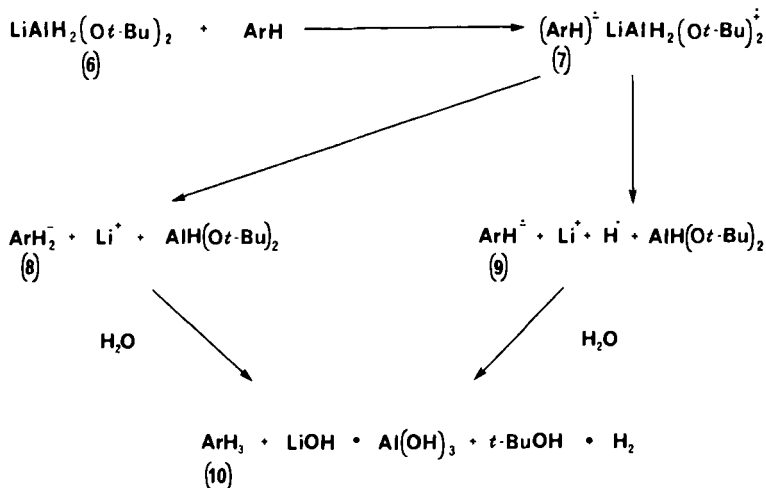
⁶ A. B. Uzienko and A. A. Yasnikov, *Ukr. Khim. Zh. (Russ. Ed.)* **38**, 1289 (1972).

⁷ E. C. Ashby and A. B. Goel, *Tetrahedron Lett.*, 4783 (1981).

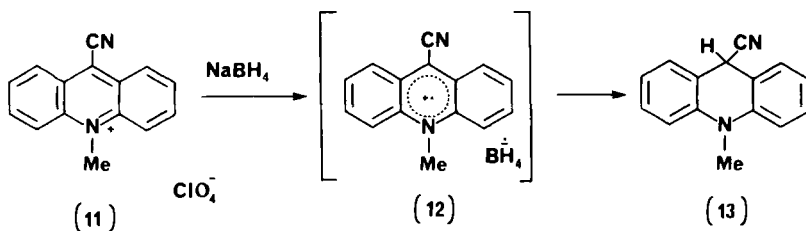
⁸ P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.* **85**, 2236 (1963).



concentration of observable radical intermediates. It was suggested that the initial radical pair that was formed (7) underwent not only further reaction to the reduced product 8 but also dissociation to the free radical anion 9.⁷



Sosonkin and co-workers have recently shown that the ESR signal obtained on reduction of 9-cyano-10-methylacridinium perchlorate (11) with NBH was identical with that produced by electrochemical (one-electron) reduction of the same cation in dimethylformamide.⁹



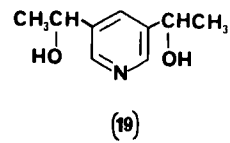
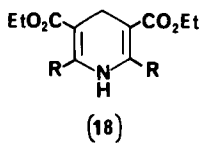
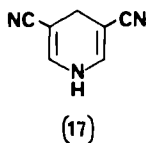
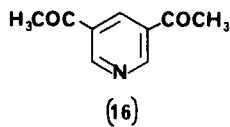
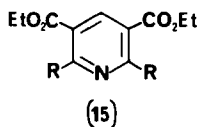
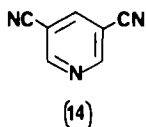
⁹ I. M. Sosonkin, A. I. Matern, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.* **10**, 1377 (1983).

III. Reduction of Heterocycles Containing One Nitrogen Atom

A. PYRIDINES

1. With Borohydride

The reduction of pyridines with NBH occurs only if they carry electron-withdrawing substituents. Most pyridines containing a single electron-withdrawing substituent in the 2 or 4 position are unaffected by NBH. Reaction, if any, occurs at the substituent.¹⁰ However, a single electron-withdrawing group in the 3 position can lead to ring reduction.¹¹ 3,5-Dicyano- (14)¹² and 3,5-diethoxycarbonylpyridine (15) were among the first to be studied in detail.¹³ Reduction leads mainly to mixtures of the 1,2- and 1,4-dihydro species. In pyridine, the 1,4-dihydropyridines are favored.¹⁴ Sodium cyanoborohydride affords the 1,4-dihydropyridine 18 in high yield (~80%), essentially free from the 1,2-dihydro analog. Reduction of 3,5-diacetylpyridine (16) with NBH and LAH gives the 3,5-diol 19 in 98% yield. A small amount of nuclear reduction is observed (~2%), of which the major component was determined spectrophotometrically to be the 1,4-dihydro isomer.¹⁵



¹⁰ Y. Kikugawa, M. Kuramoto, I. Saito, and S.-I. Yamada, *Chem. Pharm. Bull.* **21**, 1927 (1973).

¹¹ Y. Kikugawa, M. Kuramoto, I. Saito, and S.-I. Yamada, *Chem. Pharm. Bull.* **21**, 1914 (1973).

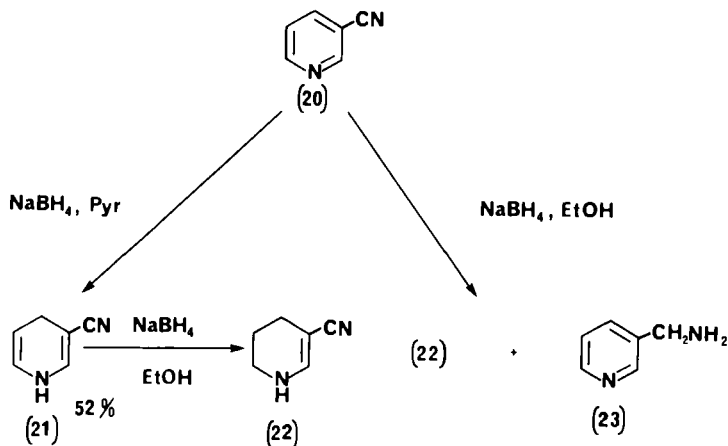
¹² J. Kuthan and E. Janeckova, *Collect. Czech. Chem. Commun.* **29**, 1654 (1964).

¹³ P. J. Brignell, U. Eisner, and P. G. Farrell, *J. Chem. Soc. B*, 1083 (1966).

¹⁴ E. Booker and U. Eisner, *J. C. S. Perkin I*, 929 (1975).

¹⁵ J. Palecek, L. Vavruska, and J. Kuthan, *Collect. Czech. Chem. Commun.* **37**, 2764 (1972).

The reduction of 3-cyanopyridine (**20**) in ethanol leads mainly to the tetrahydropyridine **22**.¹⁶ Reduction in pyridine or diglyme however, produces 1,4-dihydropyridine (**21**) as the major product. Minor amounts of the 3-pyridylmethylamine **23** are also obtained with ethanol, and the aprotic solvents prevent further ring reduction.



Reduction of 2- and 4-cyanopyridines with NBH in pyridine or diglyme might be expected to give the aminomethyl compounds. However, 2-cyanopyridine (**24**) gives in diglyme a 20% yield of 2,4,5-tris-2-pyridylimidazole (**26**).¹⁶ 4-Cyanopyridine (**25**) on reduction in pyridine gave low yields of 2,4,5-tris-4-pyridylimidazole (**27**) and 1,1-bis-4-pyridylmethylamine (**28**). The formation of such products possibly involves a benzoin type coupling of the initially formed aldimine, which can then undergo further reaction with another molecule of cyanopyridine. In ethanol, substituent reactions predominate on NBH reduction. 2-Cyanopyridine gives the amine **29** and amidine **30**. 4-Cyanopyridine gives the amine **29** in 53% yield.¹⁰

The reduction of nicotinamide (**31**) with NBH in diglyme at 140°C gave a low yield of tetrahydropyridine (**22**) and the piperidine **32**. Addition of ethanol as a proton source raised the yield of **22** to 42%.^{11,17} The dehydration of primary amides with borohydride is known to occur in moderate yield.¹⁸

The reduction of 2-alkylamino- and 2-arylino-3,5-dinitropyridines (**33**) in water leads to the tetrahydropyridines **34** in high yields.^{19,20} The

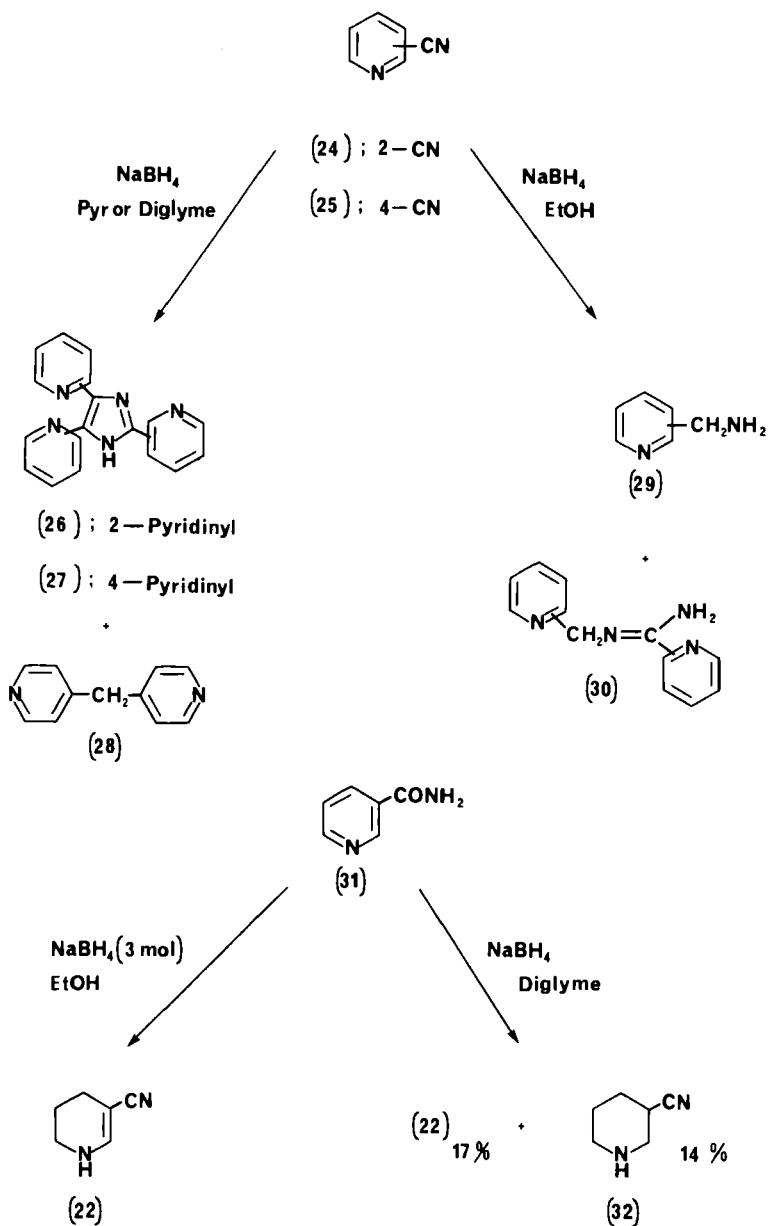
¹⁶ S.-I. Yamada, M. Kuramoto, and Y. Kikugawa, *Tetrahedron Lett.*, 3101 (1969).

¹⁷ Y. Kikugawa, S. Ikegami, and S.-I. Yamada, *Chem. Pharm. Bull.* **17**, 98 (1969).

¹⁸ V. M. Micovic and M. L. J. Mihailovic, *J. Org. Chem.* **18**, 1190 (1953).

¹⁹ A. Signor, A. Orto, and A. Marzotto, *Atti Accad. Peloritana Pericolanti, Cl. Sci. Fis., Mat. Nat.* **50**, 85 (1970).

²⁰ A. Signor and E. Bordignon, *Tetrahedron* **24**, 6995 (1968).



NaBH_4 (3 mol)
 EtOH



(22)

NaBH_4
 Diglyme

(22) 17% + (32) 14%

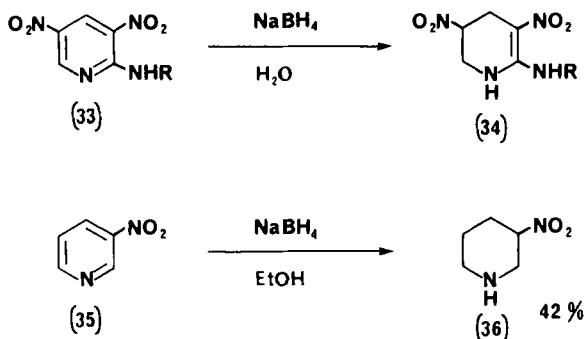


(32)

precise nature of the products was confirmed, and the mechanism was proposed on the basis of experiments using deuterated reagents.²¹ 3-Nitropyri-

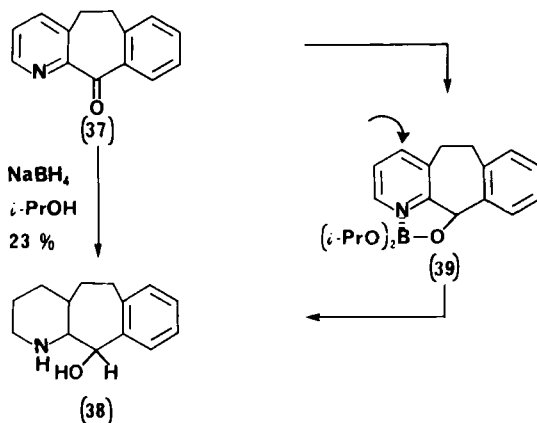
²¹ E. Bordignon, A. Signor, I. J. Fletcher, A. R. Katritzky, and J. R. Lea, *J. Chem. Soc. B*, 1567 (1970).

dine (35) was reduced to the piperidine 36 with borohydride, an indication that initial attack occurs at the 4 position.¹¹ Pyridine 3-carboxylic acid derivatives and 3-halopyridines are normally unreactive toward borohydride.¹¹



An interesting occurrence is the complete reduction of the pyridine ring in 5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (37) to the piperidine 38 in 2-propanol with NBH_4 .²²

The *cis* isomer was favored ($\sim 9:1$). This is a rare example of deactivated pyridine undergoing borohydride reduction. The answer lies in the carbonyl group, which undoubtedly undergoes reduction to give the borate ester 39. This boron complex will have a significant steric requirement. It is known that increasing the size of the 1 substituent increases the proportion of hydride attack at the 4 position, and hence formation of piperidine, in pyridinium salts.²³ Likewise, initial hydride attack will now be directed toward the 4 position, and subsequently the piperidine 38 will be formed.

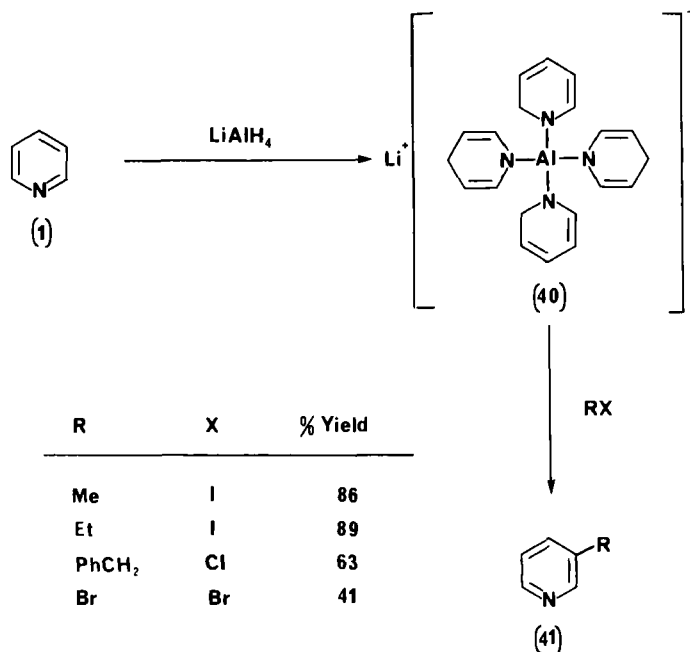


²² J. A. Bristol and C. Puchalski, *J. Org. Chem.* **45**, 4206 (1980).

²³ P. S. Anderson, W. E. Krueger, and R. E. Lyle, *Tetrahedron Lett.*, 4011 (1965).

2. With Aluminum Hydrides

Lithium aluminum hydride (LAH) reductions are carried out in aprotic solvents and give rise to the dihydro- and tetrahydropyridine derivatives. LAH reacts with both pyridines and pyridinium salts.¹ It has been known for some time that aged (~24 h) pyridine and LAH solutions form complexes of lithium tetrakis(*N*-dihydropyridinyl)aluminate (**40**, LDPA),^{24,25} which is believed to consist of a mixture of the 1,2- and 1,4-dihydropyridines (by NMR). Indeed, LDPA itself has been used as a selective reducing agent for ketones²⁴ and affords 3-substituted pyridines (**41**) on reaction with alkyl halides.²⁶ 2,5-Dihydropyridines have been identified as intermediates in similar reactions.²⁷ Kuthan and co-workers have shown that for 3,5-dicyan-



pyridine (**14**) the rate of reduction was faster in ether than in THF, but the ratio of isomers was not altered.²⁸ For lithium and sodium aluminum hydrides and sodium diethoxyaluminum hydride, $\text{NaAlH}_2(\text{OEt})_2$, approxi-

²⁴ C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.* **93**, 1294 (1971).

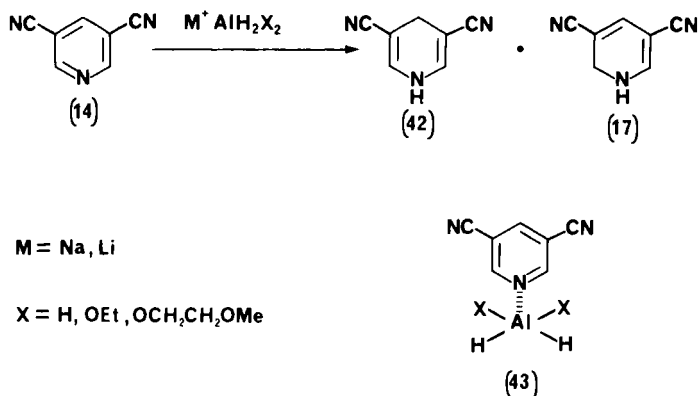
²⁵ P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.* **84**, 1756 (1962).

²⁶ R. F. Francis, C. D. Crews, and B. S. Scott, *J. Org. Chem.* **43**, 3227 (1978).

²⁷ R. F. Francis, W. Davis, and J. T. Wisener, *J. Org. Chem.* **39**, 59 (1974).

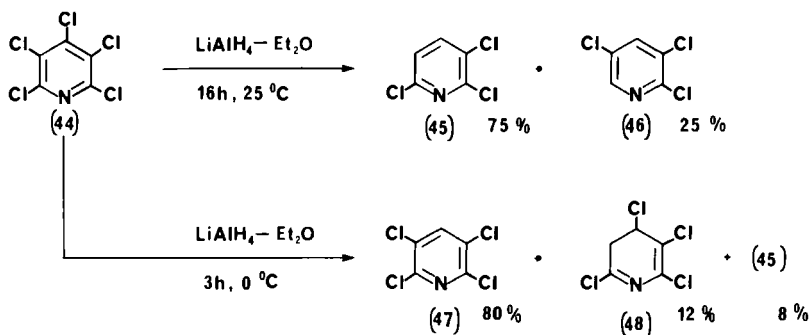
²⁸ J. Kuthan, J. Prochazkova, and E. Janeckova, *Collect. Czech. Chem. Commun.* **33**, 3558 (1968).

mately 1 : 1 mixtures of 1,2- and 1,4-dihydro-3,5-dicyanopyridines (**42** and **17**) are isolated. When sodium bis-(1,4-dioxapentyl)aluminum hydride [$\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$] was used, only the 1,4-dihydro compound **17** was isolated in low yield.²⁸ This can be explained by the formation of an initial coordination complex between the hydride reagent and the pyridine **43**. Attack at the 2 position is favored for $\text{X} = \text{H}$, but when $\text{X} = \text{OCH}_2\text{CH}_2\text{OCH}_3$, steric effects make this more difficult, and reduction occurs at the 4 position.



The preference for α attack occurs due to the N–Al interaction, aided by the metal d orbitals from which hydride transfer can be considered as occurring favorably to these positions.²⁸

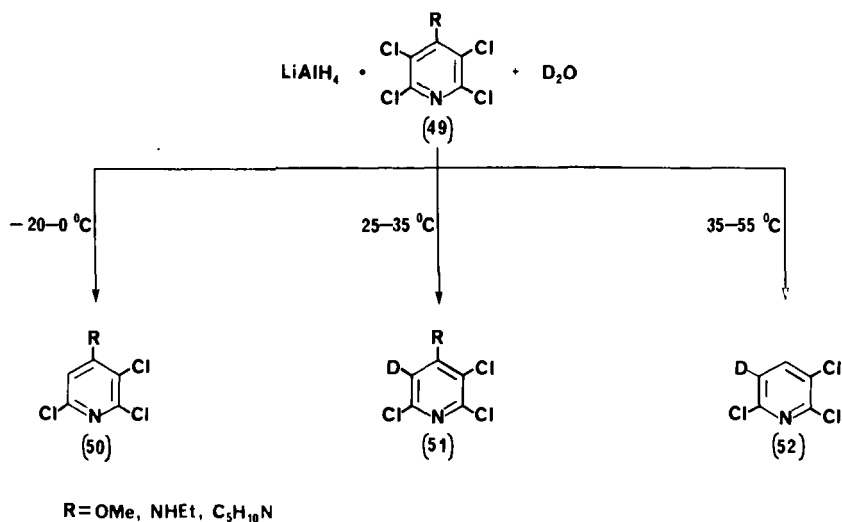
Pentachloropyridine (**44**) gives mainly 2,3,6-trichloropyridine (**45**) on treatment with LAH at room temperature.^{29,30} No products of ring reduction are observed, and the reactions are believed to proceed via an addition–elimination mechanism. The chlorine atom prevents additions at the 1,2



²⁹ F. Binns, S. M. Roberts, and H. Suschitzky, *J. C. S. Chem. Commun.*, 1211 (1969).

³⁰ F. Binns, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc. C*, 1375 (1970).

and 1,4 positions. 4-Substituted tetrachloropyridines (49) give different products (50, 51, 52) at different temperatures.³⁰



3. Other Hydrides

Magnesium³¹ and zinc hydrides³² have both been reported to form bis(di-hydropyridinyl) complexes when dissolved in pyridine. Both have been used as reducing agents for ketones, nitriles, and heterocyclic systems.³¹ Nuclear magnetic resonance studies on these complexes have shown only signals due to 1,4-dihydropyridines.³² The formation of 1,2-dihydropyridines, obtained on dissolving MgH_2 in pyridine,³³ was attributed to contamination by aluminum hydride.³⁴ Cyclic trimeric structures for these magnesium and zinc hydride complexes have been proposed in agreement with spectral data.³²

B. PYRIDONES

1. With Aluminum Hydrides

Most of the work concerning the reduction of pyridones has been carried out by Ferles and Holik, using 1,X-dimethyl-2-pyridones. Reaction of 1-

³¹ A. J. de Koning, P. H. M. Budzelaar, B. G. K. van Aarssen, J. Boersma, and G. J. M. van der Kerk, *J. Organomet. Chem.* **217**, C1 (1981).

³² A. J. de Koning, J. Boersma, and G. J. M. van der Kerk, *Tetrahedron Lett.*, 2547 (1977).

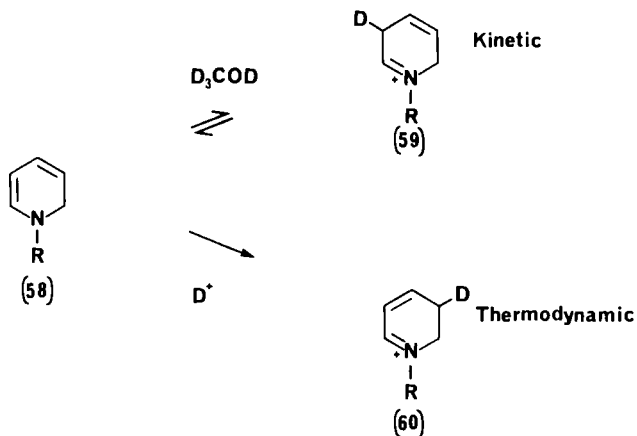
³³ E. C. Ashby and A. B. Goel, *J. Organomet. Chem.* **204**, 139 (1981).

³⁴ G. D. Barbaras, C. Dillard, A. E. Finholt, T. Wartik, K. E. Wilzbach, and H. I. Schlesinger, *J. Am. Chem. Soc.* **73**, 4585 (1951).

reactions occur initially by single-electron transfer followed by proton transfer.^{42,43}

Pyridinium salts can initially give three different products on borohydride attack, the 1,2-, 1,4-, and 1,6-dihydropyridines. Invariably, mixtures are obtained, and it should be noted that in some of the early literature incorrect assignments have been made. The use of IR, UV, and high-power NMR spectroscopy has simplified the task of identification, but care should still be exercised. Initially formed adducts may also rearrange in the presence of pyridinium salts; an internal oxidation-reduction may occur affording the thermodynamically stable 1,4 isomer.^{44,45} Fowler showed in a quantitative study that 1,4-dihydropyridines are generally some 2 kcal/mol more stable than their 1,2-dihydro counterparts.^{8,46,47} The dihydropyridines formed by hydride reduction possess either an enamine or a dienamine structure. Such systems are well known to undergo attack by electrophilic reagents.⁴⁸

For 1,2(6)-dihydropyridines this can occur at two positions. Lyle has shown that protonation of the dienamine system occurs at the central atom, giving the kinetically controlled product **59**.⁴⁹ This has been described as following Ingold's rule^{50,51} in that the solvents employed, water or alcohols,



⁴² F. M. Martens and J. W. Verhoeven, *Recl. Trav. Chim. Pays-Bas* **100**, 228 (181).

⁴³ S. Yasui, K. Nakamura, and A. Ohno, *J. Org. Chem.* **49**, 878 (1984).

⁴⁴ U. Eisner and M. M. Sadeghi, *Tetrahedron Lett.*, 299 (1978).

⁴⁵ R. E. Lyle and S. E. Mallet, *Ann. N.Y. Acad. Sci.* **145**, 83 (1967).

⁴⁶ F. W. Fowler, *J. Am. Chem. Soc.* **94**, 5926 (1972).

⁴⁷ N. C. Cook and J. E. Lyons, *J. Am. Chem. Soc.* **87**, 3283 (1965).

⁴⁸ A. G. Cook, "Enamines: Synthesis, Structure and Reactions." Dekker, New York, 1969.

⁴⁹ P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964).

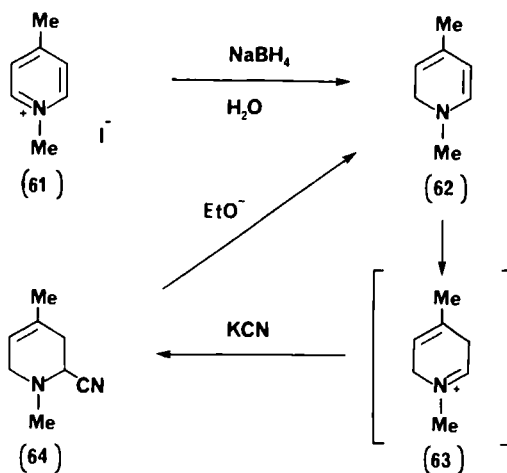
⁵⁰ N. Bodor, E. Shek, and T. Higuchi, *J. Med. Chem.* **19**, 102 (1976).

⁵¹ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 565. Cornell Univ. Press, Ithaca, New York, 1953.

are weak acids. Strong acids allow formation of the thermodynamic product **60**, i.e., protonation at the terminal carbon. Invariably the iminium salt is reduced to the tetrahydropyridine. Isomeric mixtures can result, and considerable effort has gone into the analysis and predication of the particular tetrahydropyridine formed.^{52,53}

Dihydropyridines can be isolated under appropriate sets of conditions. Use of aprotic solvents, or aqueous systems at high pH when protonation of the enamine system is less likely, favors dihydropyridine isolation. Precipitation of the dihydropyridine, or its removal from the reaction medium using two-phase systems, have been employed as techniques for their isolation.

Reductions carried out with NBH in the presence of a large excess of cyanide ion result in the formation of the 2-cyano-1,2,3,6-tetrahydropyridine **64**.⁵⁴ The 1,2-dihydropyridine **62** is regenerated on treatment with ethoxide ion. This solution to the problem of overreduction has been employed in improved syntheses of some strychnos-group alkaloids.⁵⁵



Bulky substituents attached to the ring nitrogen have been found to direct hydride attack to the 4 position, giving the 1,4-dihydropyridine.⁵⁶ Subsequent attack would lead to the piperidine, but often *p*- π interactions between the pyridine nitrogen atom and the substituent deactivate the

⁵² J. Bosch, J. Canals, E. Giralt, and R. Granados, *J. Heterocycl. Chem.* **13**, 305 (1976).

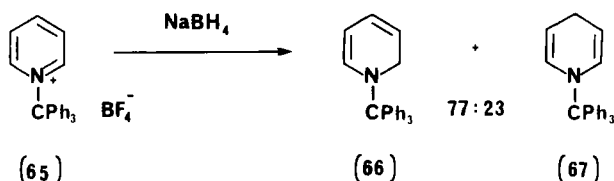
⁵³ J. Bosch, R. Granados, R. Llobera, D. Mauleon, and J. Tur, *An. Quim.* **77C**, 166 (1981).

⁵⁴ E. M. Fry, *J. Org. Chem.* **29**, 1647 (1964).

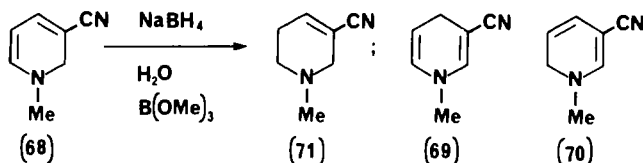
⁵⁵ J. P. Kutney, *Heterocycles* **7**, 593 (1977), and see Ref 78.

⁵⁶ R. E. Lyle and C. B. Boyce, *J. Org. Chem.* **39**, 3708 (1974).

enamine system, and dihydropyridines are isolated.^{56,57} *N*-Triphenylmethylpyridinium salts (65) give rise to this type of behavior.



Dihydropyridines generated from pyridinium salts carrying electron-withdrawing substituents at the 3 position by borohydride reduction are generally resistant to further reduction.¹ The dihydro derivatives of 1-methyl-3-cyanopyridine, 68, 69, and 70, were recovered unchanged when treated with borohydride in water.⁵⁸ Only 1,2-dihydro-1-methyl-3-cyanopyridine (68) was converted to the tetrahydropyridine 71 when trimethyl borate was added to the reaction medium. Diborane/water achieved the same conversion, while added boric acid returned the starting materials.⁵⁸



The reduction of 1-methyl-4-cyanopyridinium iodide (72) in aqueous methanol gave solely the tetrahydropyridine 73.^{59,60} However, in methanol/sodium hydroxide two different temperature-dependent products could be isolated. The [4 + 2] product 74 predominated above -20°C , whereas the [2 + 2] adduct 75 was the sole product at or below -45°C . Similar behavior is observed with the 2-cyano derivative 76 ($\text{R} = \text{H}$); again, the initially formed [2 + 2] adduct 79 ($\text{R} = \text{H}$) thermally rearranges to the [4 + 2] product 80 ($\text{R} = \text{H}$). In this case pH and temperature control are not as important because enamine reactivity is diminished by the presence of the cyano group. Other pyridinium salts behave similarly in strong base.^{61,62} Reduction

⁵⁷ A. R. Katritzky, M. H. Ibrahim, J.-Y. Valnot, and M. P. Sammes, *J. Chem. Res., Synop.*, 70 (1981).

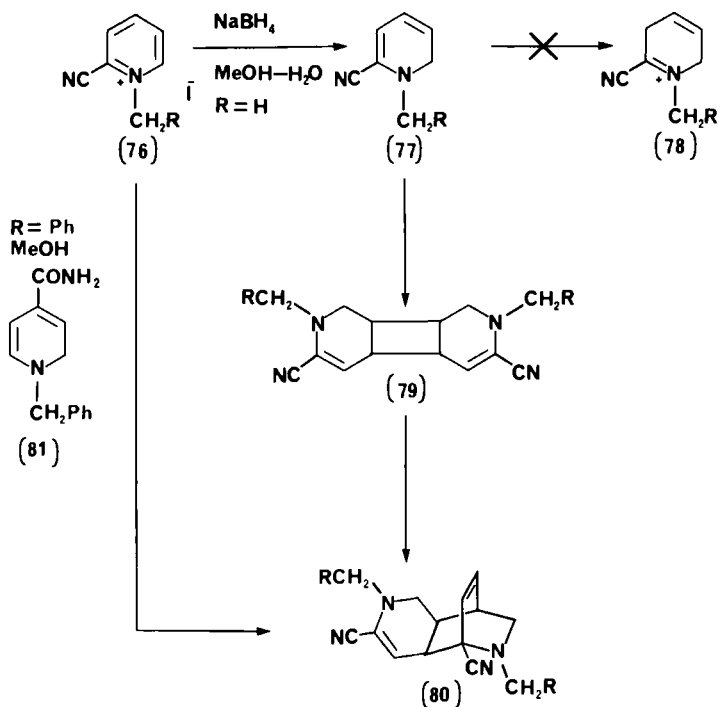
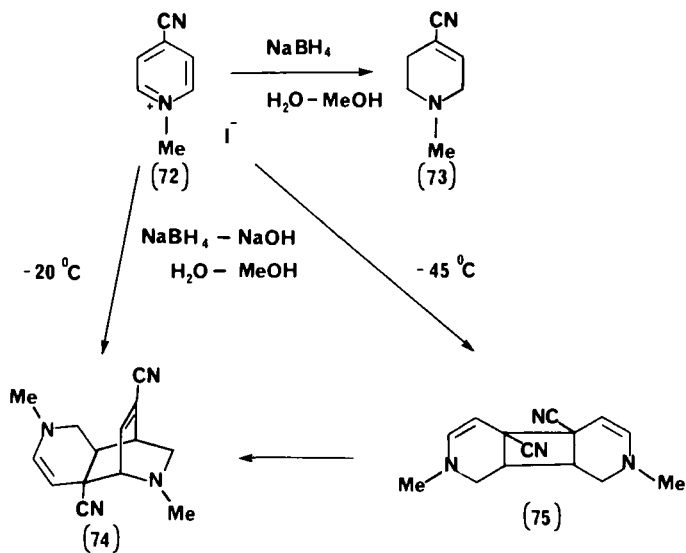
⁵⁸ F. Liberatore, V. Carelli, and M. Cardellini, *Tetrahedron Lett.*, 4735 (1968).

⁵⁹ F. Liberatore, A. Casini, V. Carelli, A. Arnone, and R. Mondelli, *Tetrahedron Lett.*, 2381 (1971).

⁶⁰ F. Liberatore, A. Casini, V. Carelli, A. Arnone, and R. Mondelli, *Tetrahedron Lett.*, 3829 (1971).

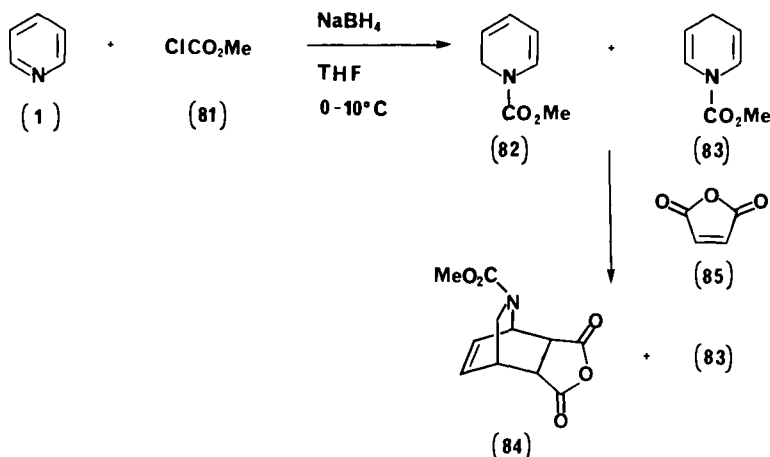
⁶¹ P. P. Zarin, E. S. Lavrinovich, and A. K. Aren, *Khim. Geterotsikl. Soedin.*, 104 (1974).

⁶² P. P. Zarin, E. E. Liepin, E. S. Lavrinovich, and A. K. Aren, *Khim. Geterotsikl. Soedin.*, 115 (1974).

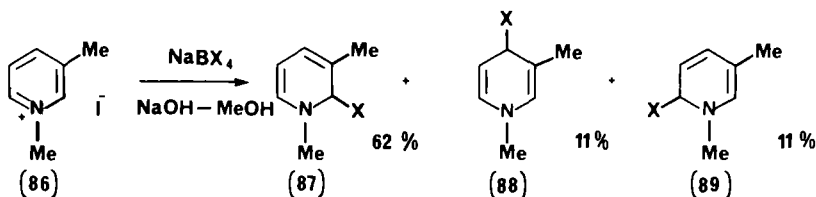


of 1-benzyl-2-cyano pyridinium salts (**76**, R = Ph) with 1-benzyl-1,2-dihydroisnicotinamide (**81**) in methanol affords the similar dimeric dihydropyridine **80**, (R = Ph).⁶³

The propensity of 1,2-dihydropyridines to undergo the Diels–Alder reaction has been used to separate mixtures of 1,2 and 1,4 isomers.^{64,65} Fowler separated out 1,4-dihydropyridines by reaction of the 1,2 isomer **82** with maleic anhydride (**85**).⁶⁶ Other workers have utilized the Diels–Alder adducts **84** in the synthesis of isoquinuclidines.⁶⁷



The reduction of pyridinium salts **86** with borohydride in methanolic sodium hydroxide gives mixtures of di- and tetrahydropyridines (**87–91**).⁶⁸ Over time, the dimeric species **91** increased, while **87** decreased.



⁶³ A. Nuvole, G. Paglietti, P. Sanna, and R. M. Acheson, *J. Chem. Res., Synop.*, 356 (1984).

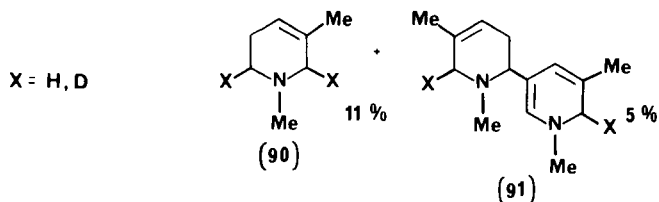
⁶⁴ E. E. Knaus, F. M. Pasutto, and C. S. Giam, *J. Heterocycl. Chem.* **11**, 843 (1974).

⁶⁵ E. E. Knaus, F. M. Pasutto, C. S. Giam, and E. A. Swinyard, *J. Heterocycl. Chem.* **13**, 481 (1976).

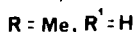
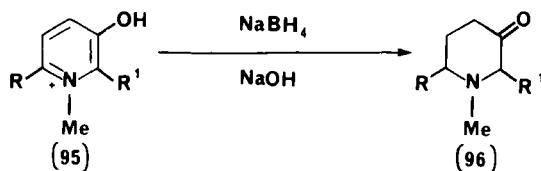
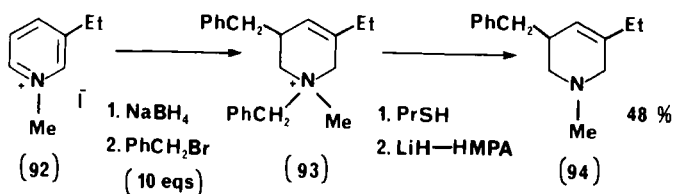
⁶⁶ F. W. Fowler, *J. Org. Chem.* **37**, 1321 (1972).

⁶⁷ G. R. Krow, J. T. Carey, D. E. Zacharias, and E. E. Knaus, *J. Org. Chem.* **47**, 1989 (1982).

⁶⁸ A. Casini, B. Di Rienzo, F. M. Moracci, S. Tortorella, F. Liberatore, and A. Arnone, *Tetrahedron Lett.*, 2139 (1978).



The reduction of 1-methyl-3-ethylpyridinium iodide (92) in the presence of a large excess (10 equiv) of benzyl bromide led to a moderate yield of 1-methyl-3-ethyl-5-benzyl-1,2,5,6-tetrahydropyridine (94),^{69,70} presumably via the 1,2-dihydropyridine. 1,6-Dimethyl-3-hydroxypyridinium iodide (95) undergoes reduction with NBH and sodium hydroxide to the 3-piperidinol 96.⁷¹



Comins reported the regiospecific addition of hydride ion to the 4 position of 1-acylpyridinium salts in moderate yields, but with high selectivity (> 90%).⁷² The copper hydride reagent used was prepared *in situ* from lithium tri-*tert*-butoxyaluminum hydride and cuprous bromide. 1-(Phenoxy-carbonyl)pyridinium chloride (97) gave the 1,4-dihydropyridine 98 exclu-

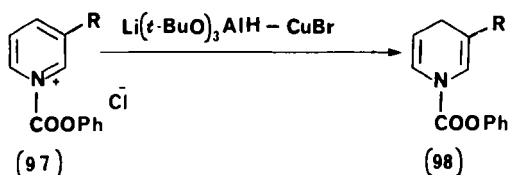
⁶⁹ J. P. Kutney, M. Noda, and B. R. Worth, *Heterocycles* **12**, 1269 (1979).

⁷⁰ J. P. Kutney, R. Greenhouse, and V. E. Ridauro, *J. Am. Chem. Soc.* **96**, 7364 (1974).

⁷¹ M. A. Iorio, F. Gatto, and H. Michalek, *Eur. J. Med. Chem.* **15**, 165 (1980).

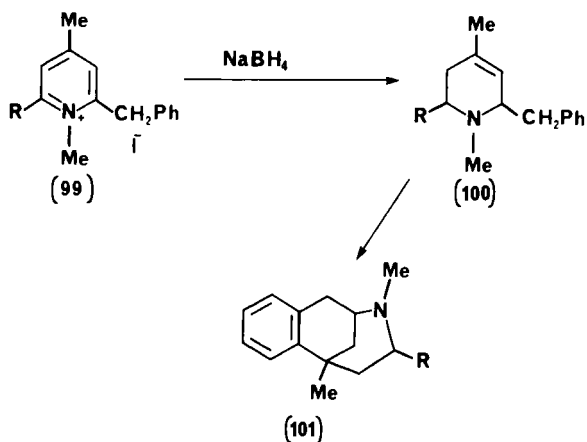
⁷² D. L. Comins and A. H. Abdullah, *J. Org. Chem.* **49**, 3392 (1984).

sively. Previous work had shown that reduction with NBH and sodium and lithium copper hydrides yields mixtures of 1,2- and 1,4-dihydropyridines.⁷³



R = H, Me, Et, Cl, CO₂Me Selectivity = 90-100 %
Yield = 40-65 %

The acid-induced cyclization of 2-(arylmethyl)tetrahydropyridines (**100**) has been used as a general method for the preparation of benzomorphans⁷⁴ (**101**) and their heterocyclic counterparts. Similar behavior is used in the



formation of the indole alkaloid (±)-dasycarpidone (**103**).⁷⁵⁻⁷⁷ Preparation of these tetracyclic substrates can be achieved more conveniently via 2-cyano-1,2,3,6-tetrahydropyridines (**105** → **107**), which are masked 2,5-dihydropyridinium salts as discovered by Fry.^{54,78}

⁷³ R. J. Sundberg and J. D. Bloom, *J. Org. Chem.* **46**, 4836 (1981).

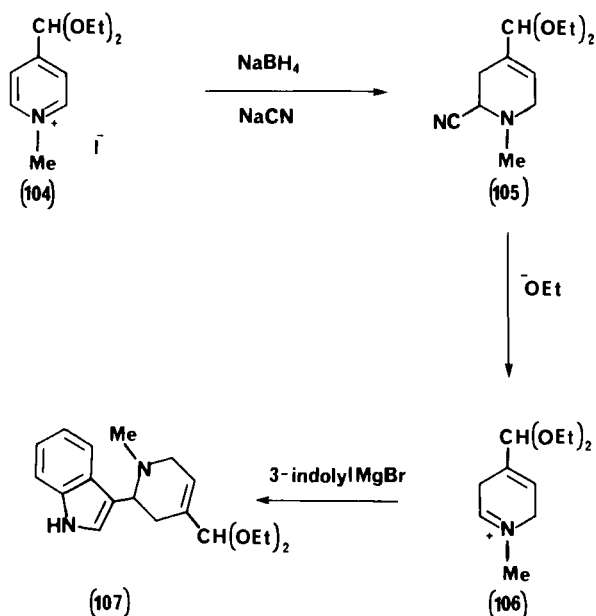
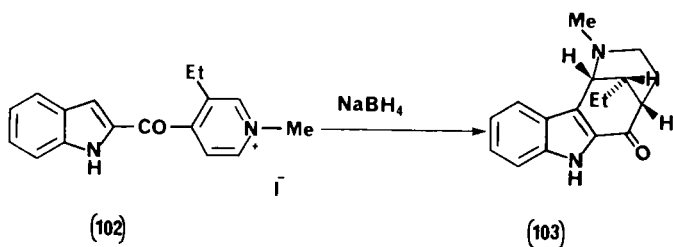
⁷⁴ J. Bosch, D. Mauleon, F. Boncompagni, and R. Granados, *J. Heterocycl. Chem.* **18**, 263 (1981).

⁷⁵ A. Jackson, A. J. Gaskell, N. D. V. Wilson, and J. A. Joule, *J. C. S. Chem. Commun.*, 364 (1968).

⁷⁶ M. S. Allen, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc. C*, 736 (1971).

⁷⁷ A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc. C*, 2738 (1969).

⁷⁸ M. Feliz, J. Bosch, D. Mauleon, M. Amat, and A. Dominguez, *J. Org. Chem.* **47**, 2435 (1982).



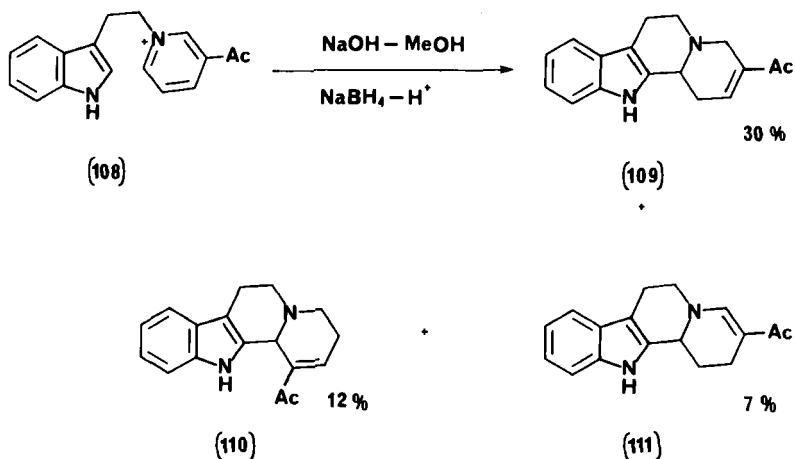
Often indolo[2,3-*a*]quinolizines (e.g., **109**) form the skeletal basis for work in the indole and oxindole alkaloid field.⁷⁹ These are most often prepared from pyridinyl- (**108**) or quinolinylindolethanes via reduction with metal hydrides.^{79,80} The tetrahydropyridines then undergo acid-catalyzed ring closure, often giving mixtures of several compounds (**109**, **110**, **111**).

The reduction of *N*-iminopyridinium salts and their ylides (**112**) has been studied and found to parallel the behavior of *N*-alkylpyridinium salts.⁸¹ In protic solvents reduction leads to the formation of 1,2,3,6-tetrahydro deriva-

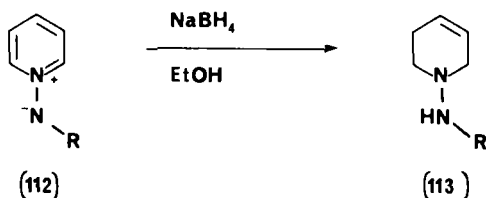
⁷⁹ M. Lounasmaa and M. Puhakka, *Acta Chem. Scand., Ser. B* **B32**, 216 (1978).

⁸⁰ W. R. Ashcroft and J. A. Joule, *Tetrahedron Lett.*, 2341 (1980).

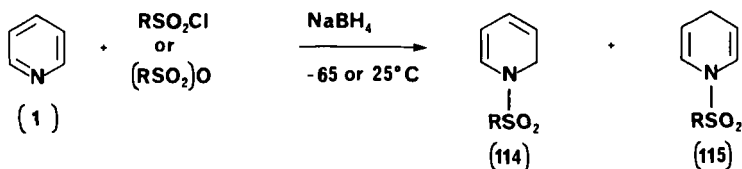
⁸¹ E. E. Knaus and K. Redda, *J. Heterocycl. Chem.* **13**, 1237 (1976).



tives (113). A probable intermediate is the 1,2-dihydro species, which, when it bears suitable substituents, may be isolated.⁸² Products of this type have shown analgesic and antiinflammatory activity.



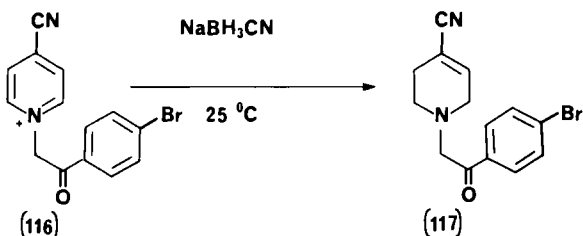
The *in situ* preparation of N-sulfonylpyridinium salts and their concomitant reduction in the presence of NBH has been studied. Using both sulfonyl chlorides and sulfonic acid anhydrides, Knaus and Redda obtained mixtures of both the 1,2- (114) and 1,4-dihydropyridines (115). The 1,4-dihydropyridine was favored (15:8 by NMR) at 25°C in pyridine; the 1,2-dihydro product was the major isomer (29:4 by NMR) at -65°C in methanol.⁸³



⁸² Y. Tamura and M. Ikeda, *Adv. Heterocycl. Chem.* **29**, 71 (1981).

⁸³ E. E. Knaus and K. Redda, *Can. J. Chem.* **55**, 1788 (1977).

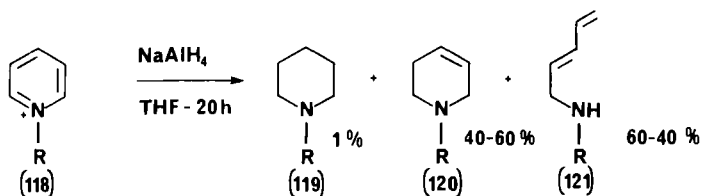
Sodium cyanoborohydride is a more selective reducing agent than borohydride.⁸⁴ An investigation into the reduction of 4-substituted pyridinium salts (116) would seem to bear this out. With these the 4 substituent directs hydride attack to the α positions, and in protic solvents the tetrahydropyridines 117 are isolated. Thus a variety of sensitive substituents can be carried through a synthetic sequence without reduction.⁸⁵ However, raising the temperature is known in one instance (4-carboxamido) to cause concomitant reduction of the ketone carbonyl group.



2. With Aluminum Hydrides

Pyridinium salts react more readily with LAH than do pyridines, affording mixtures of di- and tetrahydropyridines. However, prolonged heating of alkylpyridinium salts with excess sodium aluminum hydride in tetrahydrofuran generates 3-piperidienes (120) with 5-alkylamino-1,3-pentadiene (121) as the major products. Small amounts of the piperidines (119) were also obtained. Similar behavior has been noticed with other alkylpyridinium salts.⁸⁶

Attempts to add one equivalent of hydrogen to the 3-oxidopyridinium salts 122 led to a mixture of products, the main component being the tetrahydro derivative 123 (R = Ph, indolyl-3-ethyl) or the dimer 124 (R = Me).⁸⁷



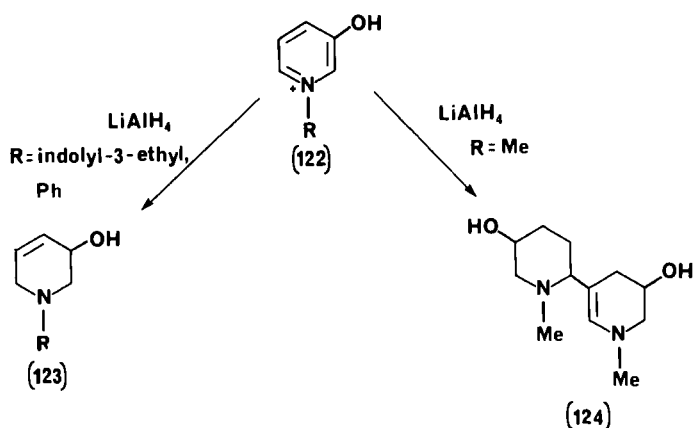
R = Et, Pr, Bu, Am.

⁸⁴ C. F. Lane, *Synthesis*, 135 (1975).

⁸⁵ R. O. Hutchins and N. R. Natale, *Synthesis*, 281 (1979).

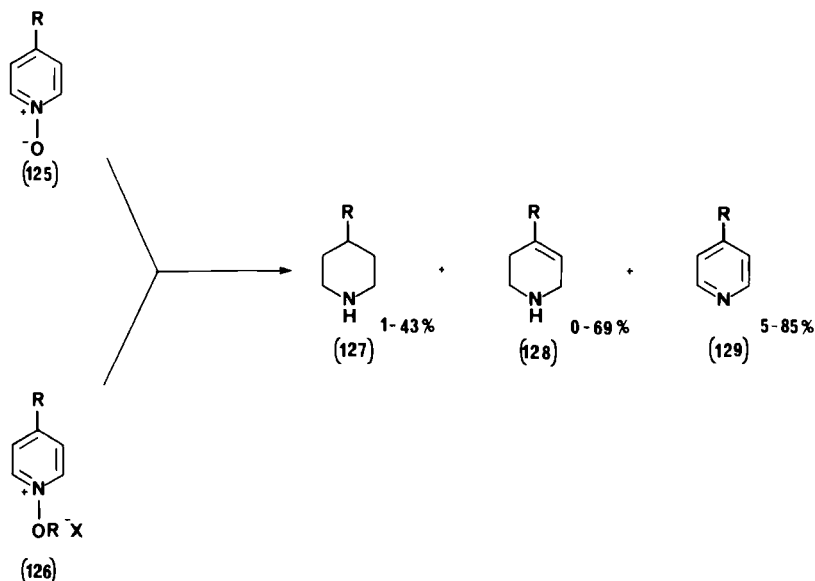
⁸⁶ M. Ferles, O. Kocian, and A. Silhankova, *Collect. Czech. Chem. Commun.* **39**, 3532 (1974).

⁸⁷ W. R. Ashcroft and J. A. Joule, *Heterocycles* **16**, 1883 (1981).



D. 1-ALKOXPYRIDINIUM SALTS AND PYRIDINE 1-OXIDES

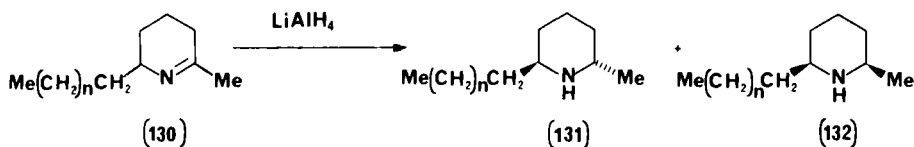
The reduction of pyridine *N*-oxide (125) and 1-alkoxypyridinium salts (126) with a variety of reducing agents, including NBH, LAH, and sodium bis(2-methoxyethyl)aluminum hydride, gives a mixture of products. The mixtures contained pyridines (129), 3-piperidine (128), and piperidines (127). The major product was dependent on the nature of the substituents



present and the reducing agent employed.⁸⁸ Titanium tetrachloride and NBH mixtures have been employed for the deoxygenation of heteroaromatic amine oxides.⁸⁹

E. CYCLIC IMINES

Cyclic imines will not be dealt with in this review as the conversion is often simply achieved.¹ Mention will be made to the stereoselective reduction involved in the preparation of Solenopsin A and B (**131**), two naturally occurring piperidine alkaloids isolated from the venom of the fire ant. The desired trans isomer **131** was obtained with >95% selectivity, using LAH (7 equiv) and trimethylaluminum (7 equiv) in THF. This selectivity could be reversed by using LAH (7 equiv) and NaOMe (14 equiv).⁹⁰



Solenopsin A, $n = 10$

Solenopsin B, $n = 12$

F. QUINOLINES

1. With Borohydrides

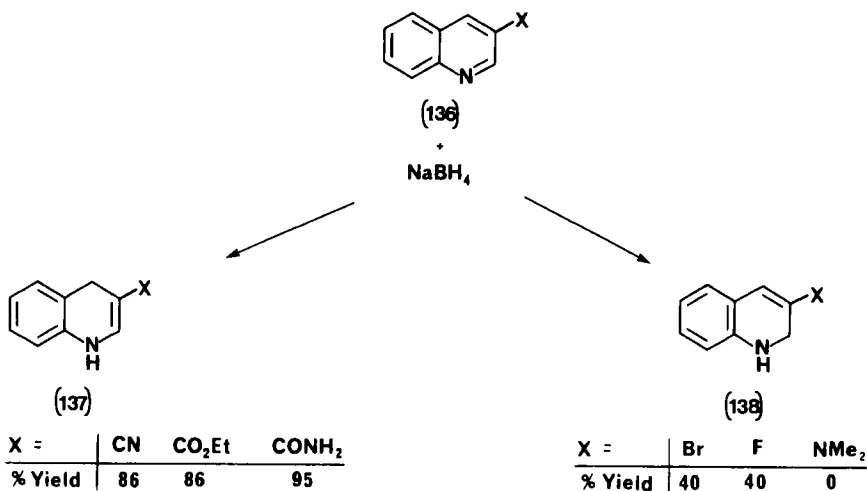
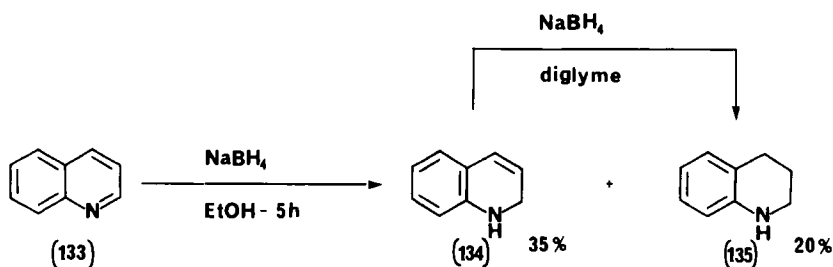
Quinolines are expected to be reduced much more readily than pyridines. This is borne out when quinoline (**133**) is heated in ethanol with excess NBH to give mixtures of the 1,2-di- **134** and 1,2,3,4-tetrahydroquinolines **135**.¹⁰ Treatment of the 1,2-dihydroquinoline **134** with NBH in diglyme or diglyme/ethanol mixtures gave conversion to the tetrahydroquinoline **135**. Migration of the 3,4 double bond to the enamine has been proposed to account for this reduction.¹¹ With electron-withdrawing groups in the 3 position, 1,4-dihydroquinolines **137** were obtained in high yields. 3-Haloquinolines, on the other hand, gave low yields of the 1,2-dihydro adducts

⁸⁸ M. Jankovsky and M. Ferles, *Collect. Czech. Chem. Commun.* **35**, 2802 (1970).

⁸⁹ S. Kano, Y. Tanaka, and S. Hibino, *Heterocycles* **14**, 39 (1980).

⁹⁰ Y. Matsumura, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, 1929 (1982).

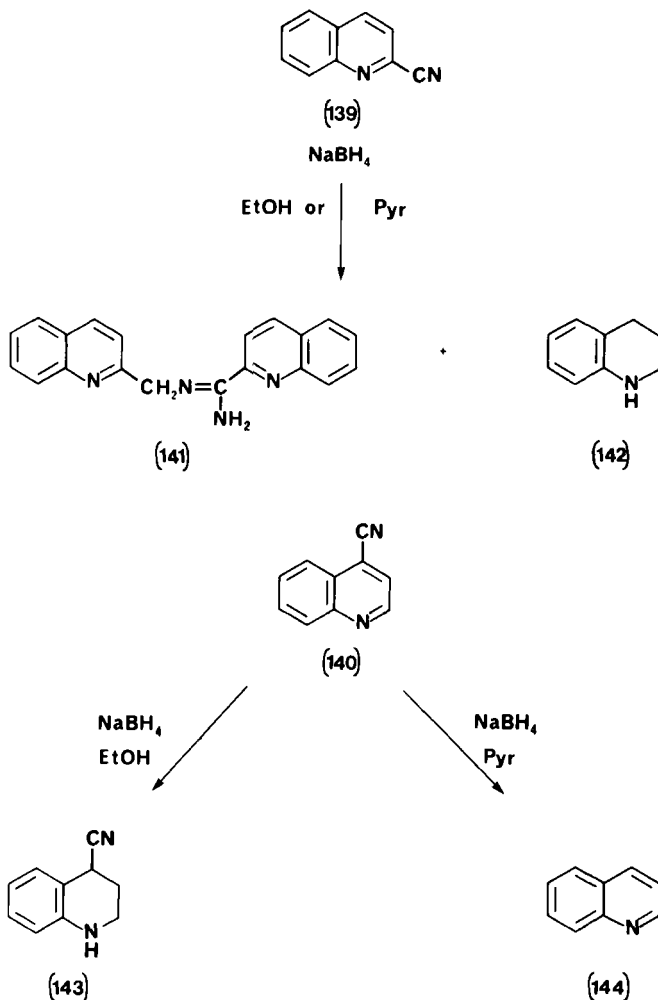
138.^{10,11} 3-Dimethylaminoquinoline was recovered unchanged under these conditions.



2-Cyanoquinoline and the 4 isomer afforded different products when reduced in ethanol or pyridine. In hot ethanol the amidine **141** was the major product, whereas in pyridine the tetrahydroquinoline **142** was favored. The latter compound occurred with an increase in tar formation. 4-Cyanoquinoline (**140**) was reduced to give the tetrahydro derivative **143** and the product of reductive decyanation **144**.^{10,11}

Reduction of 5-, 6-, 7-, and 8-nitroquinolines (**145**) with NBH in acetic acid proceeds smoothly to the 1,2-dihydro derivatives **146**.⁹¹ Gribble and

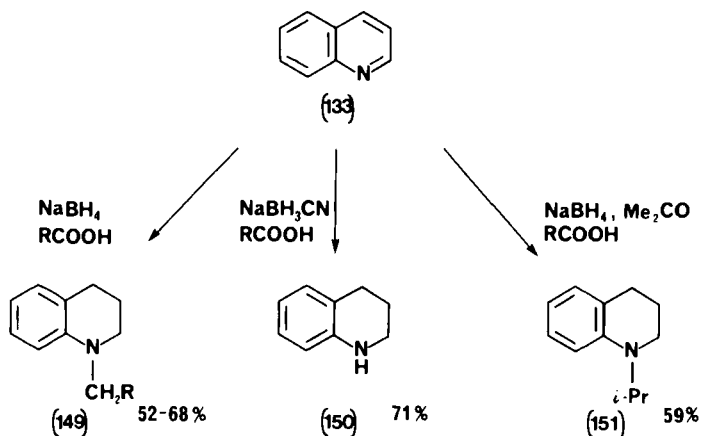
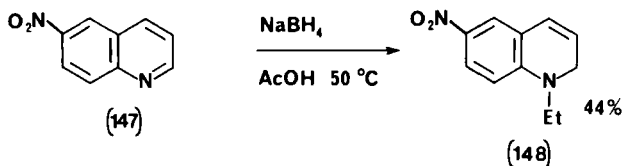
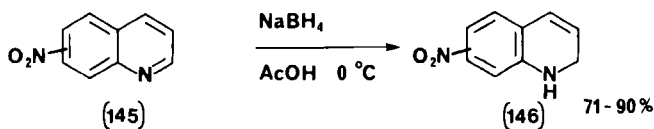
⁹¹ K. V. Rao and D. Jackman, *J. Heterocycl. Chem.* **10**, 213 (1973).



Heald repeated the same reduction of 6-nitroquinoline (**147**) at a higher temperature and isolated 1-ethyl-1,2-dihydro-6-nitroquinoline (**148**), the product of reductive alkylation.⁹² With quinoline and NBH in carboxylic acids the *N*-alkyl-1,2,3,4-tetrahydroquinoline **149** is obtained. Use of sodium cyanoborohydride gives reduction but no alkylation (**150**). In the presence of acetone, 1-isopropyl-1,2,3,4-tetrahydroquinoline (**151**) is the predominant compound.⁹² Quinoline *N*-oxides undergo deoxygenation, and some ring reduction with NBH .⁹³

⁹² G. W. Gribble and P. W. Heald, *Synthesis*, 650 (1975).

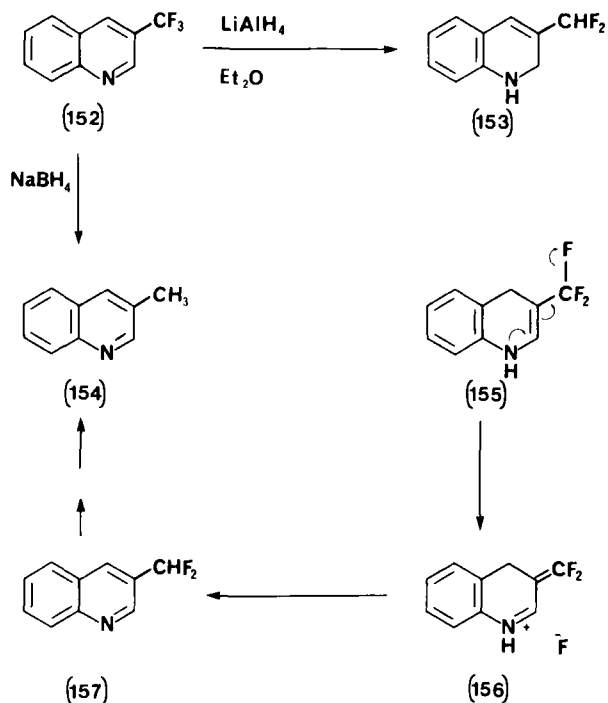
⁹³ Y. Kawazoe and M. Tachibana, *Chem. Pharm. Bull.* **13**, 1103 (1965).



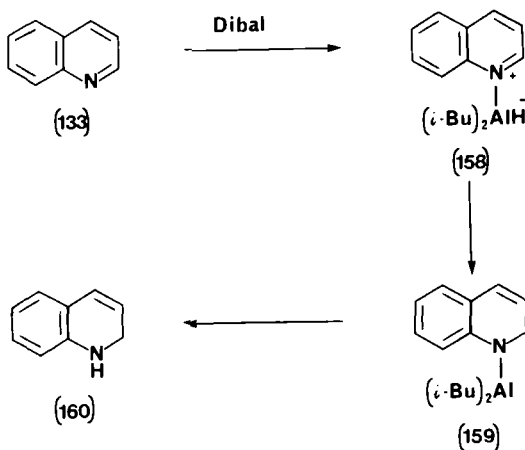
2. With Aluminum Hydrides

The 2-, 3-, 4-, and 6-trifluoromethyl derivatives of quinoline on treatment with LAH give a variety of products that depend on the position of the substituent. Only the 3 isomer **152** leads to anything other than dehalogenation, giving 3-(difluoromethyl)-1,2-dihydroquinoline (**153**).⁹⁴ On the other hand, with sodium borohydride, only **152** undergoes complete dehalogenation (**154**). This is believed to proceed via ring attack and the involvement of a 1,4-dihydroquinoline (**155**).

⁹⁴ Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* **20**, 823 (1972).



Generally, quinolines are reduced to their 1,2-dihydro derivatives with LAH. Use of diisobutylaluminum hydride and sodium bis(2-methoxyethoxy)aluminum hydride with quinoline (133) has shown that 1,2-dihydroquinolines (160) can be conveniently and cleanly generated at low tempera-

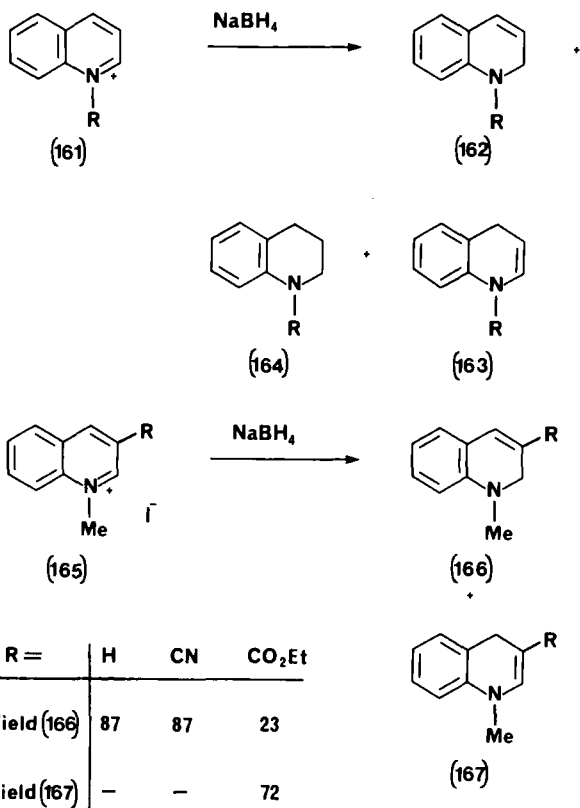


tures in high yield.^{95,96} Tetrahydroquinolines via 1,4-dihydro intermediates (thermodynamic control) are formed at higher temperatures, when prolonged reaction times are employed or when a 2 substituent is present.⁹⁶

G. QUINOLINIUM SALTS

1. With Borohydride

Like pyridinium salts, initial hydride attack can occur at either the 2 or 4 position. That the 2 position is generally favored is borne out by the isolation of 1,2-dihydroquinolines (162) as the usual products of these reductions. 1,4-Dihydro- (163) and 1,2,3,4-tetrahydroquinolines (164) formed by 4 attack are isolated as minor products.



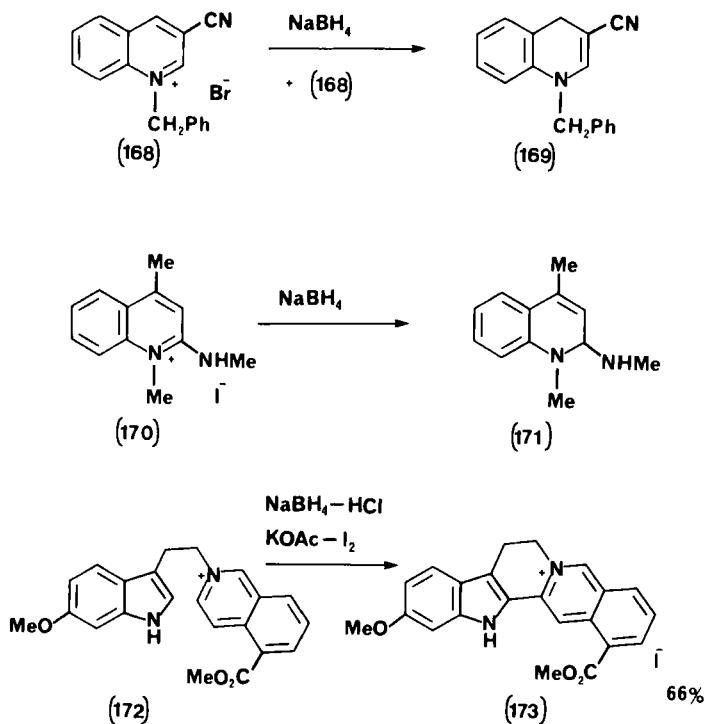
⁹⁵ D. E. Minter and P. L. Stotter, *J. Org. Chem.* **46**, 3965 (1981).

⁹⁶ B. K. Blackburn, J. F. Frysinger, and D. E. Minter, *Tetrahedron Lett.*, 4913 (1984).

Similar to the pyridinium salt series, the position and nature of substituents attached to the heteroaromatic ring can affect the position of initial attack. 1-Methylquinolinium iodide (**165**, $R = H$) gives the 1,2-dihydro adduct **166** after 10 min at $0^\circ C$, as does the 3-cyano derivative **165**, ($R = CN$).¹¹ However, under similar conditions the ethoxycarbonyl derivative **165** ($R = CO_2Et$) affords mixtures of both 1,2- (**166**) and 1,4-dihydroquinolines (**167**).¹¹

However, 1-benzyl-3-cyanoquinolinium bromide (**168**) gives a 75% yield of the 1,4-dihydro adduct **169** when reduced with $NaBH_4$ and allowed to equilibrate in the presence of the parent quinolinium salt.⁹⁷ 1,4-Dimethyl-2-methylaminoquinolinium iodide (**170**) undergoes hydride attack at the 2 position with borohydride to give the product **171** as an unstable yellow oil.⁹⁸

Alstonilin or benz[*g*]indolo[2,3-*a*]chinolizidine-type alkaloids (**173**) have been successfully prepared in high yields from the isoquinolinium salt **172** via hydride reduction.⁹⁹



⁹⁷ M. M. Kreevoy, R. M. G. Roberts, D. Ostovic, and A. D. Binder, *Ventron Alembic* **28**, 2 (1982) [*CA* **98**, 125838j (1983)].

⁹⁸ N. D. Sharma, V. K. Goyal, and B. C. Joshi, *Croat. Chem. Acta* **48**, 317 (1976).

⁹⁹ J. A. Beisler, *Chem. Ber.* **103**, 3360 (1970).

2. With Aluminum Hydrides

1,2-Dihydroquinolines predominate as the major reduction product of quinolinium salts with LAH. As in the pyridine series, preferred attack occurs at the 2 position.

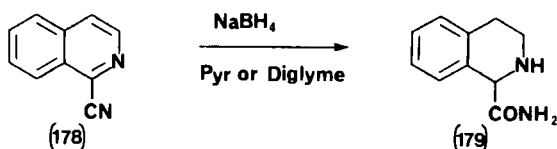
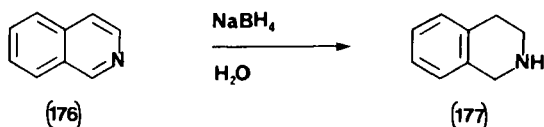
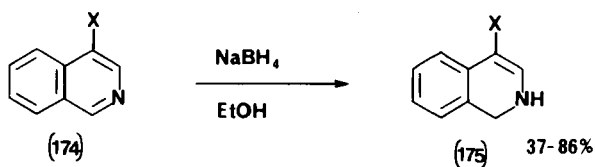
H. ISOQUINOLINES

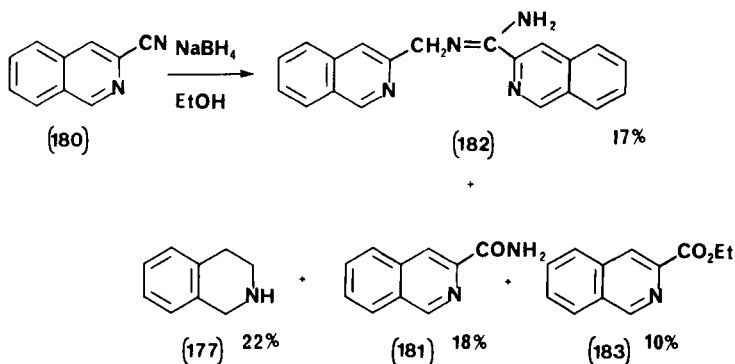
1. With Borohydrides

Isoquinolines usually do not undergo reduction with NBH in ethanol or pyridine unless they bear an electron-withdrawing 4 substituent.¹¹ In this case 1,2-dihydroisoquinolines **175** are formed.

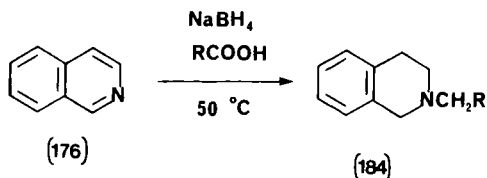
In water or aqueous solvent mixtures isoquinoline (**176**) is converted to the tetrahydroisoquinoline **177**.¹¹ In the case of 1-cyanoisoquinoline (**178**), both ring and substituent were reduced by borohydride in pyridine or diglyme.¹⁰

With 3-cyanoisoquinoline (**180**) the major products are derived from substituent reaction to form amides (**181**) and amidines (**182**). Some 1,2,3,4-tetrahydroisoquinoline (**177**) is also isolated.¹⁰ Mixtures of alcohols are obtained upon reduction of ethyl isoquinoline-2- and 3-carboxylate.¹⁰



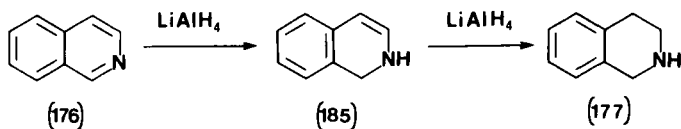


Isoquinoline (176), as in the case of quinoline, undergoes reductive alkylation with NBH in the presence of carboxylic acids, affording the amine **184**.⁹² Sodium cyanoborohydride under these conditions gave the unalkylated product **177**. Under similar conditions, but at lower temperature, 5-nitroisoquinoline affords the tetrahydroisoquinoline.⁹¹



2. With Aluminum Hydrides

As with the milder borohydride, isoquinolines are reduced to 1,2-dihydro derivatives **185** with LAH and subsequently to the tetrahydroisoquinoline **177**.

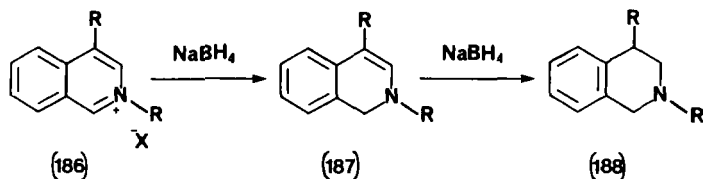


I. ISOQUINOLINIUM SALTS

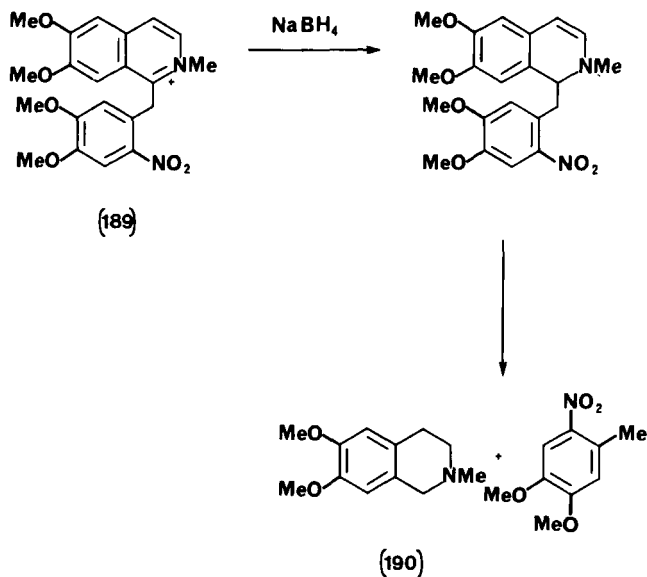
1. With Borohydride

Isoquinolinium salts (**186**) are readily reduced with NBH to the 1,2-dihydro- (**187**) or 1,2,3,4-tetrahydroisoquinolines (**188**). Initial attack occurs at

the 1 position and subsequent reduction of the enamine system is determined by the nature and position of ring substituents. Generally, tetrahydro adducts are formed.



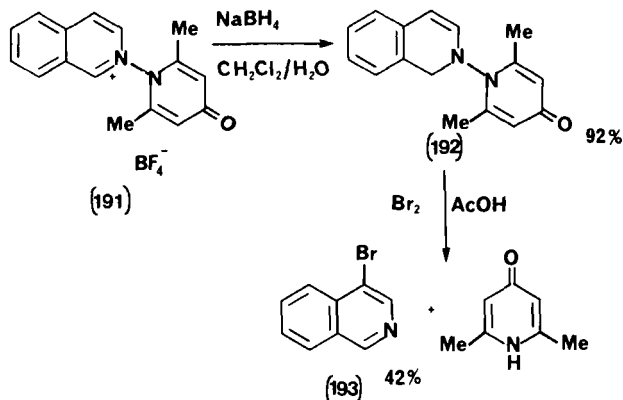
Certain 1-benzylisoquinolinium salts (189) undergo C—C bond cleavage on reduction with borohydride.^{100,101} The benzyl group must contain a nitro group in order to weaken the ring-substituent σ bond.



Reaction of the isoquinolinium salt **191** with NBH gave the 1,2-dihydroisoquinoline **192** in high yield. Subsequent treatment of **192** with bromine and heating gave 4-bromoisoquinoline (**193**).⁵⁷

¹⁰⁰ J. L. Neumeyer, M. McCarthy, K. K. Winhardt, and P. L. Levins, *J. Org. Chem.* **33**, 2890 (1968).

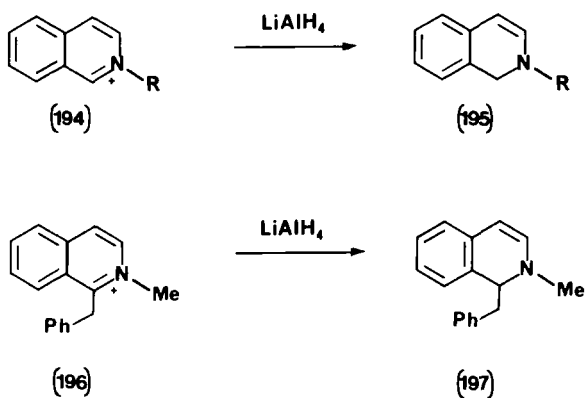
¹⁰¹ J. L. Neumeyer, M. McCarthy, and K. K. Weinhardt, *Tetrahedron Lett.*, 1095 (1967).



2. With Aluminum Hydrides

The reduction of isoquinolinium salts in aprotic solvents with LAH leads to the formation of 1,2-dihydroisoquinolines (195), in which the enamine system can undergo subsequent reaction with electrophiles. This type of reactivity has been exploited in the synthesis of alkaloids.⁵⁵

Intermediates of the types 196 and 197 have been used in synthetic approaches to the pavinane and isopavinane alkaloids.¹⁰²



J. INDOLES

Although indoles are not normally reduced under neutral conditions with LAH or NBH, tetra-*n*-butylammonium borohydride has recently been ap-

¹⁰² S. F. Dyke, R. G. Kinsman, P. Warren, and A. W. C. White, *Tetrahedron* **34**, 241 (1978).

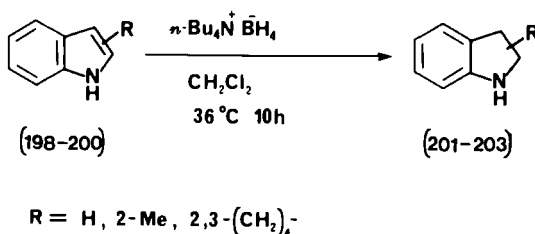
plied successfully in the reduction of the indoles **198**–**200** to indolines **201**–**203**.¹⁰³ 3-Methylindole was reduced to the indoline in only 6% yield.¹⁰³

The observation that enamines may be reduced by NBH in acetic acid/THF¹⁰⁴ and sodium cyanoborohydride¹⁰⁵ coupled with the tendency for indoles to protonate at the 3-position enabled Gribble and co-workers to reduce indoles to indolines (**201**, **205**) in high yield.¹⁰⁶ *N*-Alkyl indoles (**204**) were also reduced, as was 3-methylindole. The use of formic acid favored the formation of 1-methyl-3-[2-(2-dimethylaminophenyl)ethyl]indoline (**207**) via an intermediate 3,2 dimer (**206**).¹⁰⁷

Borohydride reduction of indole (**198**) in the presence of trifluoroacetic acid (TFA) gave the indoline **201** without alkylation but in low yield. The yield of **201** can be increased when carried out with sodium cyanoborohydride in acetic acid at 15°C. This eliminates the isolation of any *N*-alkyl indolines.¹⁰⁸

The reaction clearly proceeds via reduction of the iminium salt **208** produced on protonation, and as such the method is limited to indoles sufficiently basic to be protonated by acetic or trifluoroacetic acids.^{108–111}

The reduction of indole (**198**) has also been achieved with sodium borohydride–aluminum chloride mixtures (5:3) in pyridine at room temperature.¹¹² The pyridine serves to moderate the reducing agent and a 68% yield of indoline (**201**) was obtained along with unchanged starting material. When 2-methylpyridine replaced pyridine, no reduction was observed.



¹⁰³ T. Wakamatsu, H. Inaki, A. Ogawa, M. Watanabe, and Y. Ban, *Heterocycles* **14**, 1441 (1980).

¹⁰⁴ J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963).

¹⁰⁵ R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.* **93**, 2897 (1971).

¹⁰⁶ G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.* **96**, 7812 (1974).

¹⁰⁷ G. W. Gribble and S. W. Wright, *Heterocycles* **19**, 229 (1982).

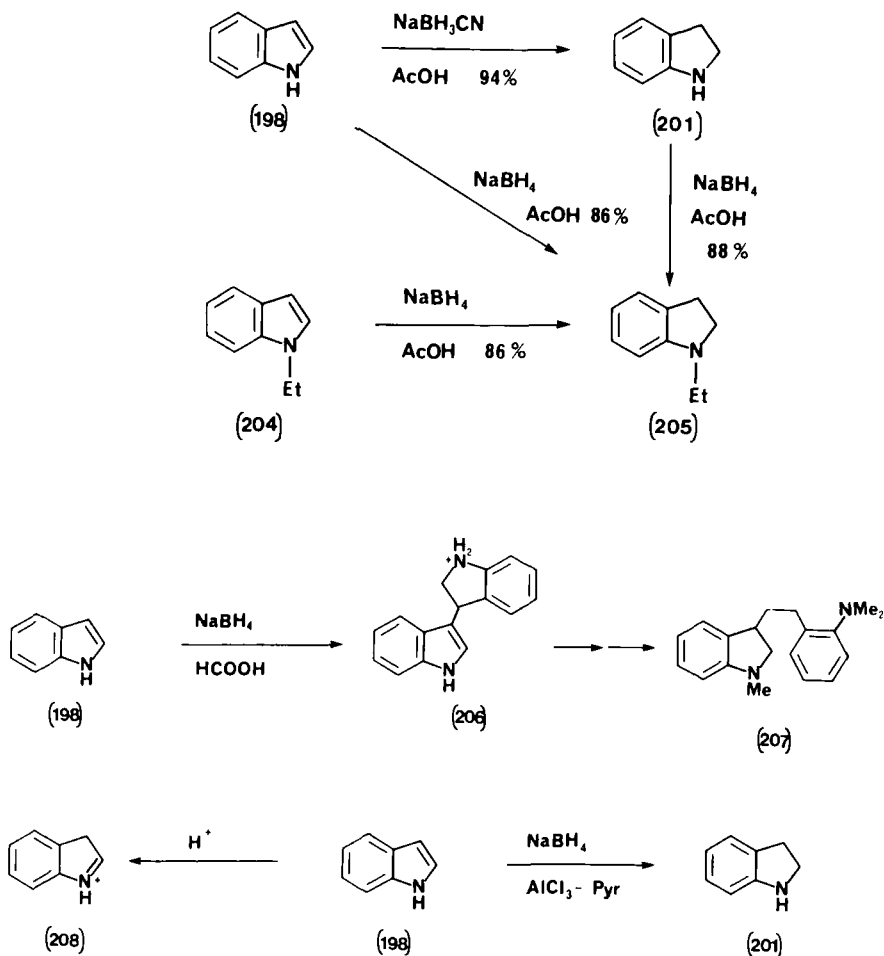
¹⁰⁸ G. W. Gribble and J. H. Hoffman, *Synthesis*, 859 (1977).

¹⁰⁹ J. G. Berger, F. Davidson, and G. E. Langford, *J. Med. Chem.* **20**, 600 (1977).

¹¹⁰ N. Umino, T. Iwakuma, and N. Itoh, *Tetrahedron Lett.*, 763 (1976).

¹¹¹ G. W. Gribble, C. F. Nutaitis, and R. M. Leese, *Heterocycles* **22**, 379 (1984).

¹¹² Y. Kikugawa, *Chem. Pharm. Bull.* **26**, 108 (1978).

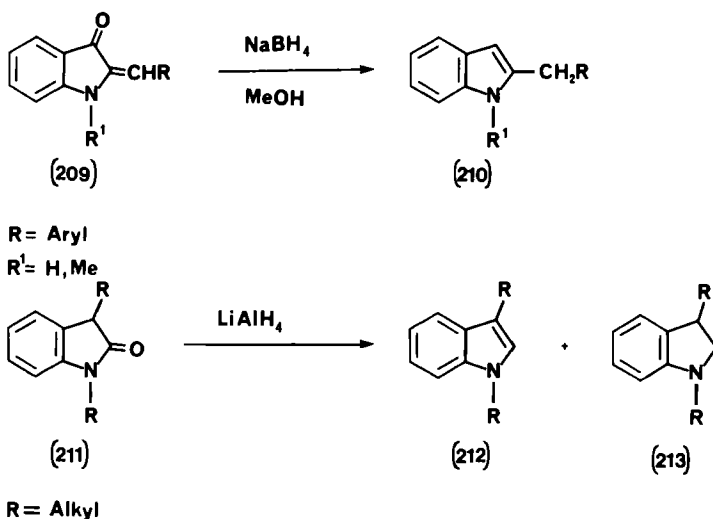


The reduction of the indolinones **209** with NBH in methanol leads readily to the indoles **210** in 56–96% yield. Intermediacy of the corresponding alcohols has been proposed.¹¹³ The reduction of indoles and related compounds has been the subject of a previous review.¹¹⁴ Oxindoles (**211**) are reduced with LAH to indoles (**212**) but in low yields.¹¹⁴ Small amounts of the indolines **213** are also obtained. Dimerization on hydride reduction has also been recorded.¹¹⁵

¹¹³ M. Hooper and W. M. Pitkethly, *J. C. S. Perkin I.* 1607 (1972).

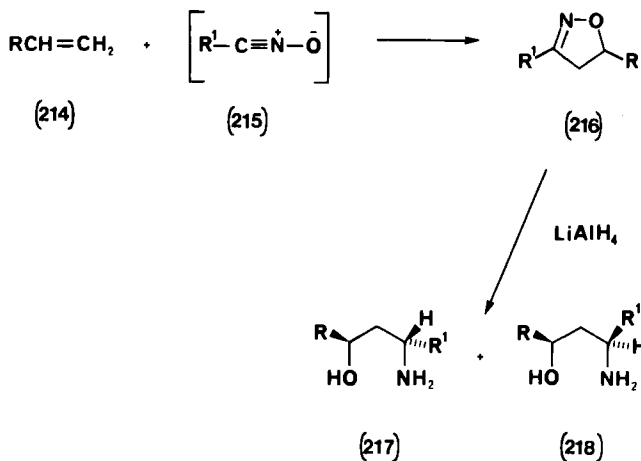
¹¹⁴ B. Robinson, *Chem. Rev.* **69**, 785 (1969).

¹¹⁵ H. J. Roth and H. H. Lausen, *Arch. Pharm. (Weinheim, Ger.)* **306**, 775 (1973).



K. 1,2-OXAZOLES

3-Aminopropanols (**217**, **218**) can be prepared from alkenes and nitrile oxides via the LAH reduction of the isoxazoline intermediate **216**.¹¹⁶ The stereospecificity of the reaction is surprisingly high. 1,3-Asymmetric induction leads to ratios of 1:19 for **217** and **218**, respectively (R = Ph) and

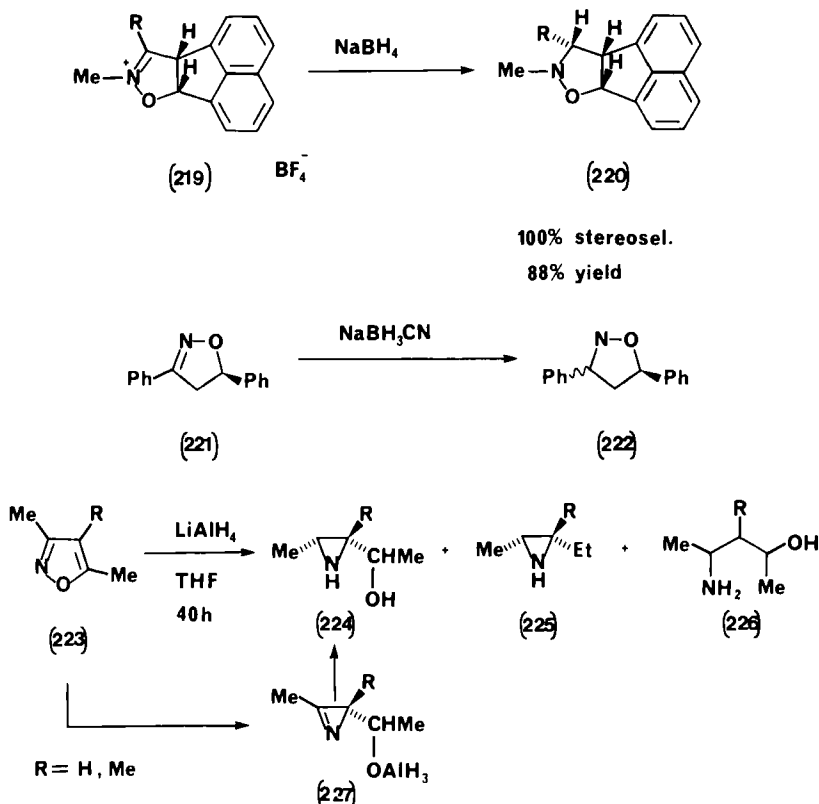


¹¹⁶ V. Jager, V. Buss, and W. Schwab, *Liebigs Ann. Chem.*, 122 (1980).

slightly less (3:17) when $R = \text{Me}$.¹¹⁷ Li-O complexation during hydride transfer is probably responsible for this selectivity.

Acyclic products are the normal result of reductions on dihydroisoxazoles with metal hydrides. However, some tetrahydro derivatives (**220**) have been produced stereoselectively upon treatment with NBH.¹¹⁸ Sodium cyanoborohydride gave *cis*- and *trans*-1,2-oxazolidines (**222**) from 3,5-diphenyl-4,5-dihydro-1,2-oxazole (**221**).¹¹⁷ 3,5-Dialkylisoxazoles with electron-withdrawing groups at C-4 can be reduced by LAH/ether and NBH/ethanol to give 4-functionalized 2-isoxazolines in 7–70% yield.^{117a}

Interestingly, alkyl-1,2-oxazoles (**223**) on reduction with LAH give aziridines **224** and **225**.¹¹⁹ Preparative chromatography was used to separate one major (**224**, 40–50%) and two minor (**225**, **226**) components. Most likely, the reaction proceeds through a hydroxyazirine intermediate (**227**).



¹¹⁷ V. Jager and V. Buss, *Liebigs Ann. Chem.*, 101 (1980).

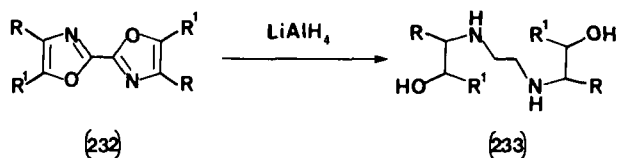
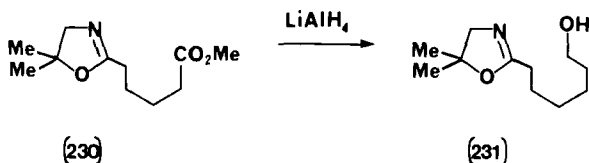
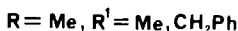
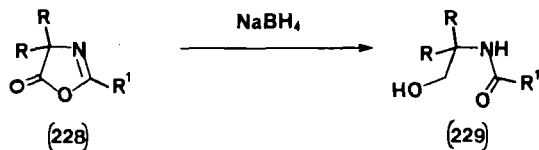
^{117a} A. Alberola, A. M. Gonzalez, M. A. Laguna, and F. J. Pulido, *Synthesis*, 413 (1983).

¹¹⁸ A. Cerri, C. De Micheli, and R. Gandolfi, *Synthesis*, 710 (1974).

¹¹⁹ A. L. Khurana and A. M. Unrau, *Can. J. Chem.* **53**, 3011 (1975).

L. 1,3-OXAZOLES

The reduction of 2-oxazolin-5-ones (**228**) with excess NBH results in the cleavage of a C—O bond to afford the amides **229**.¹²⁰ By contrast, the oxazoline moiety itself (**230**) is stable to reduction by LAH and serves as a protecting group for the carboxylic acid function.¹²¹ However, 2,2'-bis(oxazolines) (**232**) have been recorded in the patent literature as precursors to the amino alcohols **233**.¹²²



M. 1,3-THIAZOLES

3-Benzyl-4-methylthiazolium chloride (**234**) is reduced in water by excess NBH to the fully saturated 1,3-thiazolidine **237** via the thiazoline **235**.¹²³ A diastereoisomeric mixture is obtained in more highly substituted cases.¹²⁴

¹²⁰ P. Truitt and J. Chakravarty, *J. Org. Chem.* **35**, 864 (1970).

¹²¹ D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 3031 (1972).

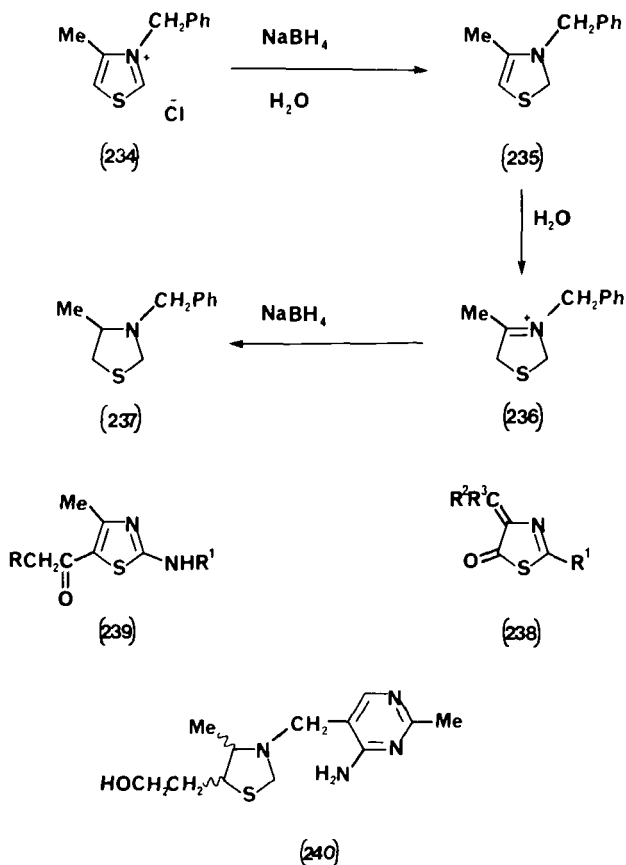
¹²² Pliva Tvrnica Farmaceut., Fr. Demande 2,187,761 (1974) [*CA* **81**, 13101f (1974)].

¹²³ G. M. Clarke and P. Sykes, *J. C. S. Chem. Commun.*, 370 (1965).

¹²⁴ G. M. Clarke and P. Sykes, *J. Chem Soc. C*, 1411 (1967).

Although, in principle, the 4-alkylidene-1,3-thiazolin-5-ones (238) can undergo initial attack at $C=O$, $C=O$ or $C=N$, in practice only the exocyclic double bond is attacked and reduced by NBH .¹²⁵

1,3-Thiazoles containing 2-amino functionalities (239) are, not surprisingly, resistant to ring reduction with NBH .¹²⁶ Thiamine is reduced to the tetrahydro derivative 240.¹²⁴



N. 1,3-THIAZINES

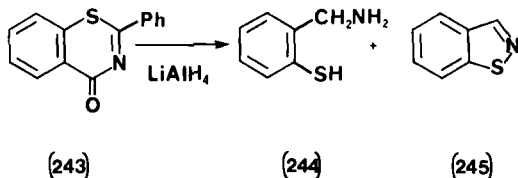
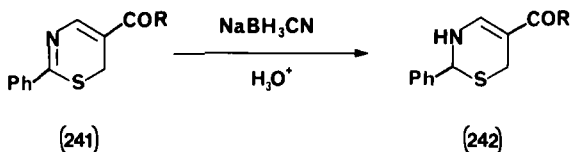
Little work has been carried out on the selective reduction of the imine bond present in 1,3-thiazines.¹²⁷ Concomitant ring opening normally occurs

¹²⁵ M. D. Bachi, *J. C. S. Perkin I*, 310 (1972).

¹²⁶ D. Suci, *J. Prakt. Chem.* **314**, 961 (1972).

¹²⁷ J.-L. Pradere, J.-C. Roze, and G. Duguay, *J. Chem. Res., Synop.*, 72 (1982).

in such systems. However, sodium cyanoborohydride will selectively reduce the imine bond in 2-phenyl-6*H*-1,3-thiazines (**241**) in acidic media.¹²⁷ This results partially from the bond polarization effects of the phenyl group and partially from protonation. More powerful reducing agents afford ring cleavage. 2-Phenyl-4-oxobenzo-1,3-thiazine (**243**) gives 2-mercaptobenzylamine (**244**) as the major product when treated with LAH.¹²⁸ The isolation of the benzothiazole **245** as a minor product points to C-2—S rupture prior to reduction of the imine.



IV. Reductions of Heterocycles Containing Two Nitrogen Atoms

A. PYRAZOLES

The LAH reduction of alkyl- and arylpyrazolium salts (**246**) has been investigated and leads to a mixture of the 3- (**247**) and 4-pyrazolines (**248**), along with the fully saturated pyrazolidine **249** in some cases.^{129,130} The exact nature of the mixture is dependent on the substituents and the amount of reducing agent employed. The 3- and 4-pyrazolines generally predominate. Overreduction with formation of acyclic hydrazines is also observed.¹²⁹ Pyrazolidines (**249**) may be produced from pyrazolines (**247** and **248**) by reduction with LAH.¹³¹

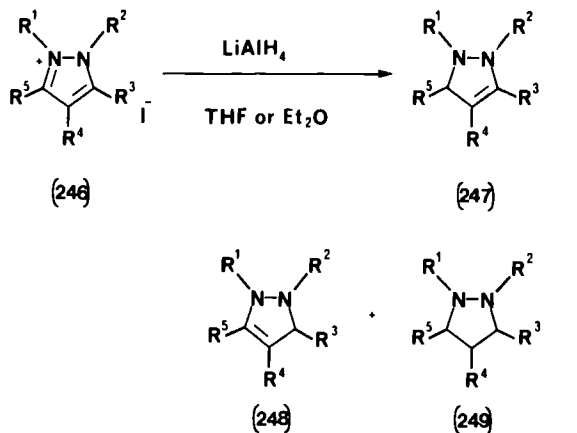
Elguero and co-workers also report the NBH and LAH reduction of

¹²⁸ D. Bourgoin-Lagay and R. Boudet, *C. R. Acad. Sci., Paris, Ser. C* **264**, 1304 (1967).

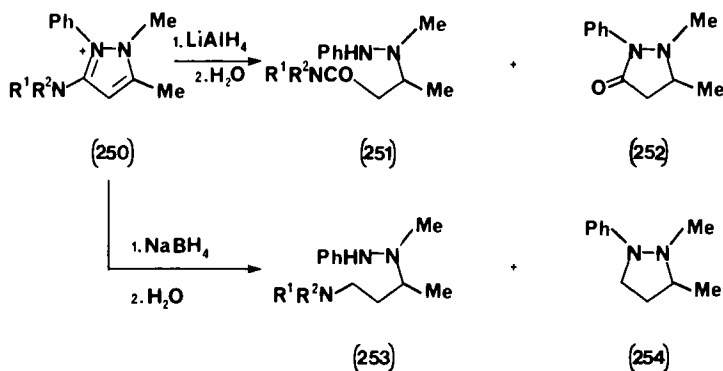
¹²⁹ J. Elguero, R. Jacquier, and D. Tizane, *Bull. Soc. Chim. Fr.*, 1121 (1970).

¹³⁰ J. Elguero, R. Jacquier, and D. Tizane, *Bull. Soc. Chim. Fr.*, 3866 (1968).

¹³¹ J. Elguero, R. Jacquier, and D. Tizane, *Bull. Soc. Chim. Fr.*, 1129 (1970).



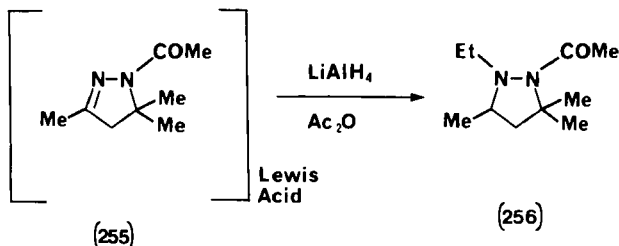
3-(disubstituted amino)-1,5-dimethyl-2-phenylpyrazolium salts (250), affording the hydrazines 251 and 253 as the major products.¹³²



(250)	R ¹	R ²	Reductant	Product (%)
a	Me	Me	LiAlH ₄	251 (80), 252 (15)
b	-CH ₂ CH ₂ OCH ₂ CH ₂ -		LiAlH ₄	251 (95)
c	Me	Ph	LiAlH ₄	251 (95)
b	-CH ₂ CH ₂ OCH ₂ CH ₂ -		NaBH ₄	253 (60), 254 (40)
c	Me	Ph	NaBH ₄	253 (90), 254 (10)

¹³² J. Elguero, R. Jacquier, and S. Mignonac-Mondon, *Bull. Soc. Chim. Fr.*, 2807 (1972).

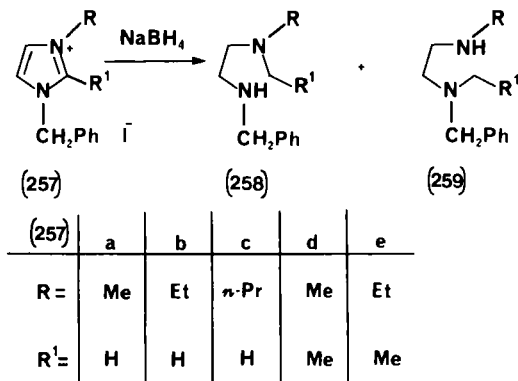
Increasing the polarization of the imine double bond by complexation of 1-acetyl-3,5,5-trimethylpyrazoline (**255**) with Lewis acids is an effective method of inducing C-3 nucleophilic attack.¹³³ LAH Reduction of **255** in acetic anhydride has the overall effect of a reductive alkylation to give 1-acetyl-2-ethyl-3,5,5-trimethylpyrazolidine (**256**). Similar behavior has been ob-



served with the hydrochloride salts of 1-phenyl- and 1,5-diphenyl-3-methyl-2-pyrazolines.¹³⁴

B. IMIDAZOLES

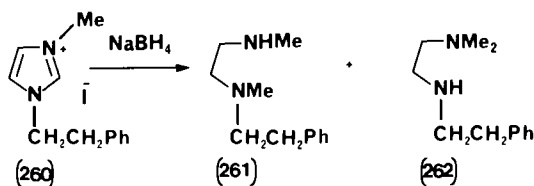
The reaction of several simple imidazolium salts (**257**) in 95% ethanol, employing a large excess of NBH, led to reductive ring cleavage to the diamines **258** and **259**.¹³⁵ The major product was **258** (77–93%) and the minor product, **259** (3–22%). Thus the predominant cleavage is between C-2 and *N*-benzyl. Similar reduction of 1-methyl-3-(2-phenylethyl)imidazolium iodide (**260**) gave **262** as the major product (92%).¹³⁵



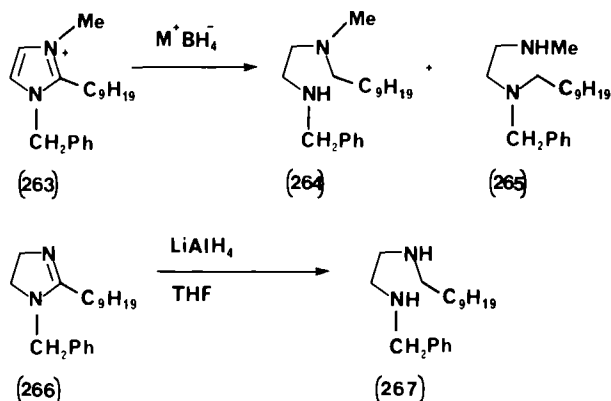
¹³³ L. A. Sviridova, G. A. Golubeva, A. V. Dovgilevich, and A. N. Kost, *Khim. Geterotsikl. Soedin.* **9**, 1239 (1980).

¹³⁴ G. A. Golubeva, L. A. Sviridova, N. Y. Lebedenko, and A. N. Kost, *Khim. Geterotsikl. Soedin.* **4**, 547 (1973).

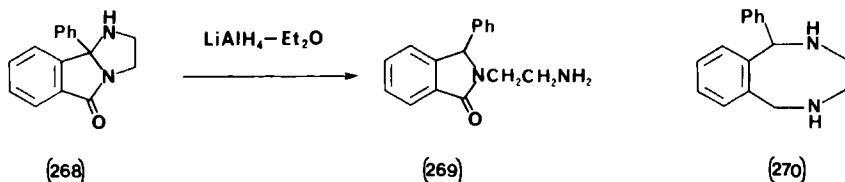
¹³⁵ E. F. Godefroi, *J. Org. Chem.* **33**, 860 (1968).



Treatment of the long-chain imidazolium salts **263** with potassium, sodium, and tetra-*n*-butylammonium borohydrides affords the acyclic diamines **264** and **265**. The isomer ratio was not reported.¹³⁶ Sodium cyanoborohydride failed to reduce the same salt under a variety of conditions. The imidazoline **266** reacts with LAH in THF above -10°C to give the 1,2-diaminoethane **267**.¹³⁶ Sodium borohydride is a less effective reducing agent in this reaction, achieving the same conversion over a longer period of time. Other less reactive hydrides [LiBH_4 , NaBH_3CN , $\text{LiAlH}(\text{O}-t\text{-Bu})_3$] do not react.¹³⁶



Reductive ring cleavage of the tetrahydroimidazole **268** has been recorded with LAH in ether.¹³⁷ Formation of the isoindolone **269** is in contrast with earlier reports in which ring expansion to the diazocine **270** was reported.¹³⁷

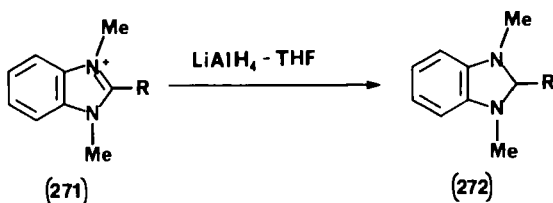


¹³⁶ M. W. Anderson, R. C. F. Jones, and J. Saunders, *J. C. S. Chem. Commun.* 282 (1982).

¹³⁷ P. Aeberli, G. Cooke, W. J. Houlihan, and W. G. Salmond, *J. Org. Chem.* **40**, 382 (1975).

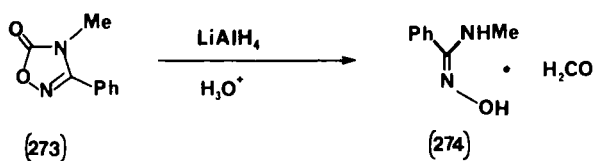
C. BENZIMIDAZOLES

The reduction of the benzimidazolium salts **271** under controlled conditions with LAH in THF has been described.¹³⁸ The resulting benzimidazolines **272** may be similarly prepared, using LAH in ether¹³⁹ or NBH in water.¹⁴⁰



D. 1,2,4-OXADIAZOLES

A variety of ureas and oximes can result from the reduction of 1,2,4-oxadiazoles with LAH. The nature and position of substituents will determine the position of the attack and hence, the product. However, the majority of products arise from cleavage of the C-5—O bond via chelation-assistance (**273** → **274**).¹⁴¹



E. PYRIDAZINES

Simple dihydropyridazines have been obtained by reduction of the parent pyridazine after initial alkylation.¹⁴² Sodium borohydride reduced the 1-methylpyridazinium salts in water to the corresponding 1,6-dihydropyridazine **276** in 40–60% yield. In some instances (**276c,e,f**) the 1,4,5,6-tetrahy-

¹³⁸ J.-L. Aubagnac, J. Elguero, R. Jacquier, and R. Robert, *Bull. Soc. Chim. Fr.*, 2184 (1971).

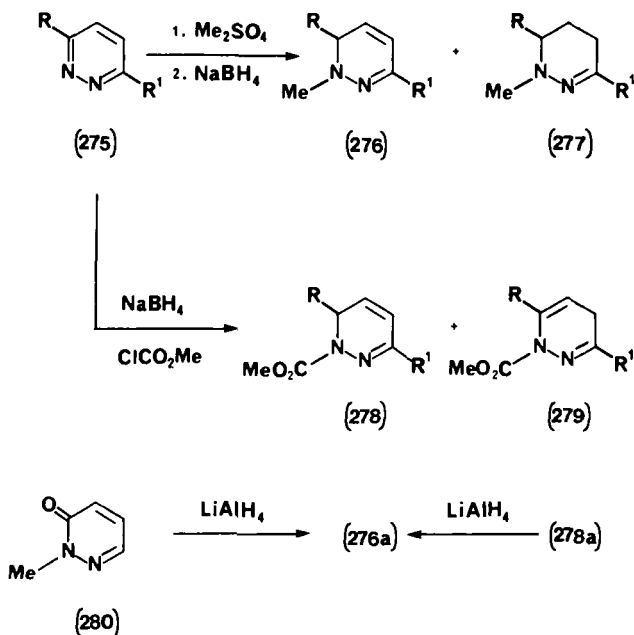
¹³⁹ A. V. El'tsov, *J. Org. Chem. USSR (Engl. Transl.)* **1**, 1121 (1965).

¹⁴⁰ J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Aust. J. Chem.* **17**, 877 (1964).

¹⁴¹ Y. Royer, M. Selim, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1060 (1973).

¹⁴² C. Kaneko, T. Tsuchiya, and H. Igeta, *Chem. Pharm. Bull.* **22**, 2894 (1974).

dropyridazines **277** were also isolated. The phenyl derivatives **276e,f** were the most stable, but all gradually decomposed when exposed to the atmosphere. 1,3,4,6-Tetraalkyl-1,6-dihydropyridazines are also available by this route.¹⁴³ Reduction of **275** with NBH in the presence of methyl chloroformate gave the 1,6-dihydro derivatives **278** in 30–50% yield along with small amounts of the 1,4 isomer **279**. These were more stable than their *N*-methyl counterparts (**276**). The presence of a phenyl group favored the 1,6-dihydropyridazines **278** and in its absence the 1,4 isomers **279a** predominated.^{142,143} Dihydropyridazine (**276a**) was also obtained by treatment of 1-methyl-6-pyridazinone (**280**) or **278a** with LAH in THF.¹⁴⁴

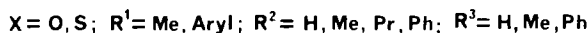
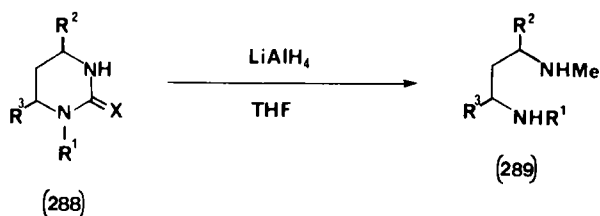


(275)	a	b	c	d	e	f
R	H	H	Me	H	H	Me
R'	H	Me	Me	OH	Ph	Ph

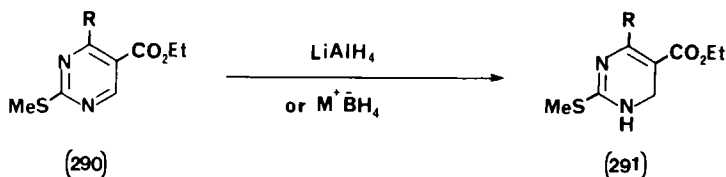
Hexahydro derivatives **283** are favored when 3 mol of LAH are allowed to react with 2,3,4,5-tetrahydropyridazin-3-ones (**281**).¹⁴⁴ Use of less reducing

¹⁴³ Y. Zenichi, Jpn. Kokai 78/44,580 (1978).

¹⁴⁴ J.-L. Aubagnac, J. Elguero, R. Jacquier, and R. Robert, *Bull. Soc. Chim. Fr.*, 2859 (1972).



recovered. Earlier, it had been found that ethyl 4-hydroxyiminomethyl-2-methylthiopyrimidine-5-carboxylate (**290a**), and subsequently other pyrimidines, underwent preferential ring reduction. Lithium aluminum hydride in pyridine, lithium borohydride in THF, and sodium borohydride in ethanol all reduced **290** to ethyl 4-substituted-2-methylthio-1,6-dihydropyrimidines (**291**). When $\text{R} = \text{SMe}$, NHMe , or NHNH_2 , reduction of the carboxylic acid ester occurs.¹⁵⁰



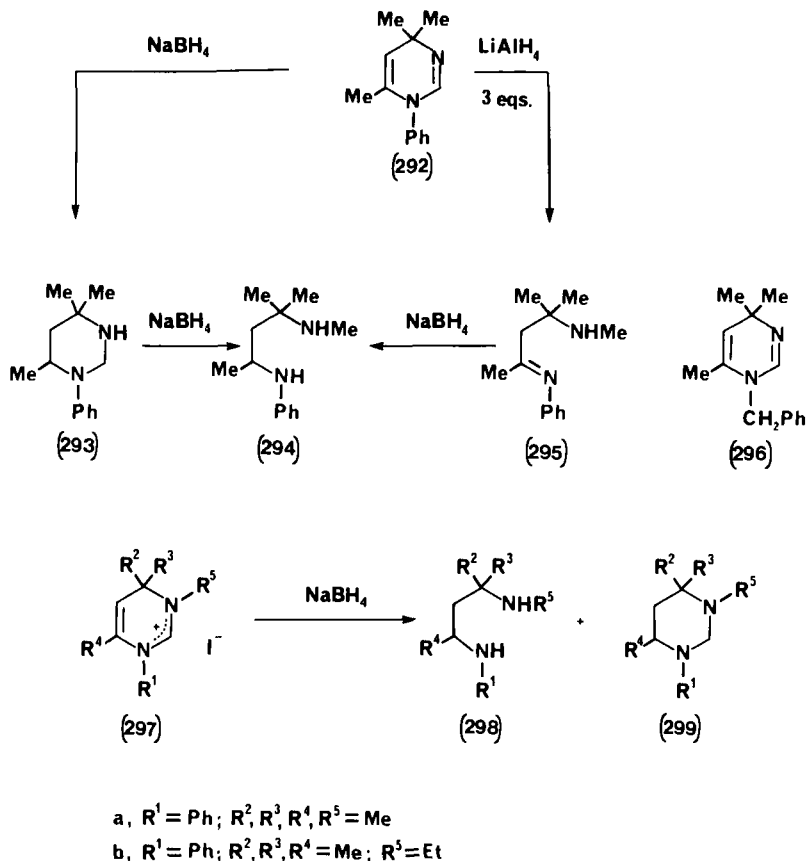
(291)	a	b	c	d	e
R	CH=NOH	CN	Me	Cl	OH

N-Substituted dihydropyrimidines on reaction with a large excess of NBH_3 in ethanol at room temperature give rise to ring-opened products (e.g., **294**).¹⁵¹ The intermediacy of the hexahydro derivative **293** was proved by its isolation from the reaction mixture and subsequent conversion to **294** with additional borohydride. 1-Phenyl-4,4,6-trimethyldihydropyrimidine (**292**) may ring open via N-1—C-2 or C-2—N-3 cleavage. In fact, only the former is observed, presumably a result of the increased stability of the N-1—phenyl anion. This is in agreement with the observation that 1-benzyl-4,4,6-trimethyl-1,4-dihydropyrimidine (**296**) gave only the hexahydro derivative in 70% yield.¹⁵¹ Surprisingly, LAH left the imine bond intact prior to ring cleavage, whereas borohydride had been demonstrated to saturate all bonds prior to opening. Alkylation and subsequent reduction of the dihydropyrimidinium salts affords mixtures of the cyclic and acyclic diamines

¹⁵⁰ R. S. Shadbolt and T. L. V. Ulbricht, *J. Chem. Soc. C*, 733 (1968).

¹⁵¹ C. Kashima, M. Shimizu, A. Katoh, and Y. Omote, *J. Heterocycl. Chem.* **21**, 441 (1984).

298 and **299**.¹⁵¹ Ring opening has also been observed in the reduction of certain 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (barbituric acid) derivatives.^{152,153}



G. PYRAZINES

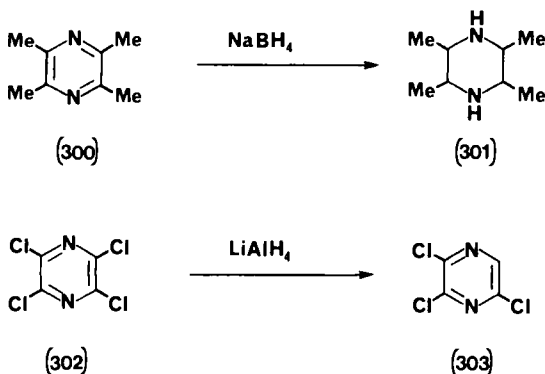
The successful trapping of the valence-bond isomer, induced during the UV irradiation of pyridine,¹⁵⁴ with NBH led to the application of this technique to 2,3,5,6-tetramethylpyrazine (**300**) Although no valence-bond iso-

¹⁵² M. Rautio, *Acta Chem. Scand., Ser. B* **B33**, 770 (1979).

¹⁵³ M. Rautio and K. Vuori, *Acta Chem. Scand., Ser. B* **B34**, 770 (1980).

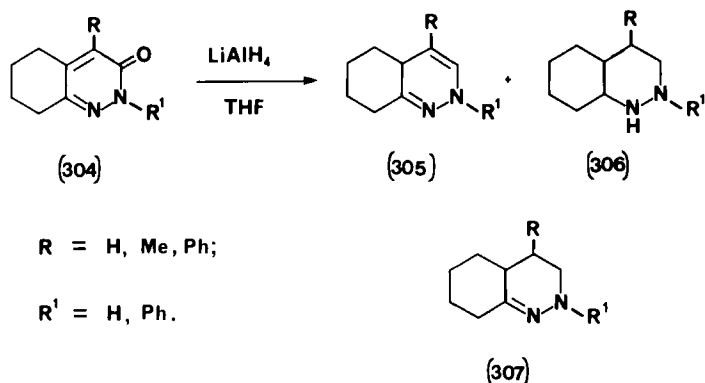
¹⁵⁴ K. E. Wilzbach and D. J. Rausch, *J. Am. Chem. Soc.* **92**, 2178 (1970).

merization was observed, hexahydropyrazine (301) was isolated.¹⁵⁵ The reduction of tetrachloropyrazine (302) with LAH affords the dehalogenated product 303.¹⁵⁶



H. CINNOLINES

On reduction with LAH, cinnolines generally yield di- and tetrahydro derivatives.^{1,157} The LAH reduction of 5,6,7,8-tetrahydro-3-cinnolinones (304) in THF leads to mixtures of the dihydrocinnolines 305, the decahydrocinnolines 306 and the deoxygenated tetrahydrocinnolines 307.¹⁵⁸ The ratio of products is dependent on the substituents and the amount of LAH used.¹⁵⁸



¹⁵⁵ D. J. Bell, I. R. Brown, R. Cocks, R. F. Evans, G. A. Macfarlane, K. N. Mewett, and A. V. Robertson, *Aust. J. Chem.* **32**, 1281 (1979).

¹⁵⁶ R. D. Chambers, W. K. R. Musgrave, and P. G. Urben, *J. C. S. Perkin I*, 2584 (1974).

¹⁵⁷ L. S. Besford, G. Allen, and J. M. Bruce, *J. Chem. Soc.*, 2867 (1963).

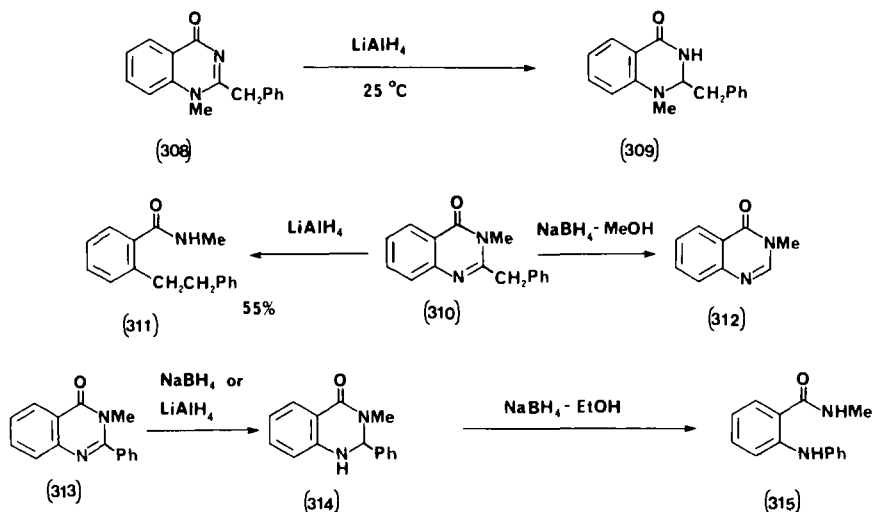
¹⁵⁸ J. Daunis, M. Guerret-Rigail, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1994 (1972).

I. QUINAZOLINES

The reductive ring cleavage that prevails with 4-quinazolinone and LAH has been the subject of several reports.¹⁵⁹⁻¹⁶² Interest was first shown after the abnormal reaction of the alkaloid 1-methyl-2-benzyl-4-quinazolinone (**308**, asborine) was found to give the 2,3-dihydro derivative **309** with the carbonyl function still intact.¹⁵⁹ However, a different orientation of the same substituents leads to the ring-opened product **311**, with cleavage occurring between C-2 and N-3 when LAH is used. In methanol, NBH gives 3-methyl-4-quinazolinone (**312**), the product of reductive debenzylation, albeit in low yield.^{159,162-164}

The position and nature of the substituents has been shown to affect the reaction markedly; for instance, NBH and LAH both generate 2-phenyl-3-methyl-1,2-dihydro-4-quinazolinone (**314**) from the parent heterocycle **313**. This compound may then be converted to the ring-cleaved product **315** on further heating with NBH in ethanol.

The 2-methyl-3-phenyl derivative with LAH gives the aniline **316** by C-2—N-3 cleavage. In the absence of the phenyl group, this cleavage occurs preferentially along the N-1—C-2 bond (**317**, 84%) along with a small amount of that derived from C-2—N-3 cleavage (**318**, 5%).¹⁶⁰



¹⁵⁹ S. C. Pakrashi and A. K. Chakravarty, *J. Org. Chem.* **37**, 3143 (1972).

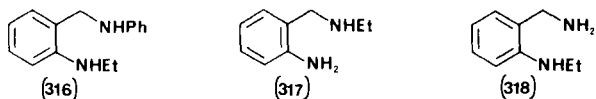
¹⁶⁰ I. R. Gelling, W. J. Irwin, and D. G. Wibberley, *J. C. S. Chem. Commun.*, 1138 (1969).

¹⁶¹ W. J. Irwin, *J. C. S. Perkin I*, 353 (1972).

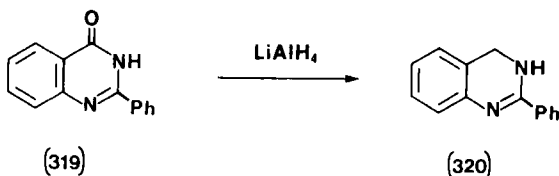
¹⁶² S. C. Pakrashi and A. K. Chakravarty, *Indian J. Chem.* **11**, 122 (1973).

¹⁶³ S. C. Pakrashi and A. K. Chakravarty, *J. C. S. Chem. Commun.*, 1443 (1969).

¹⁶⁴ N. Finch, and H. W. Gschwend, *J. Org. Chem.* **36**, 1463 (1971).



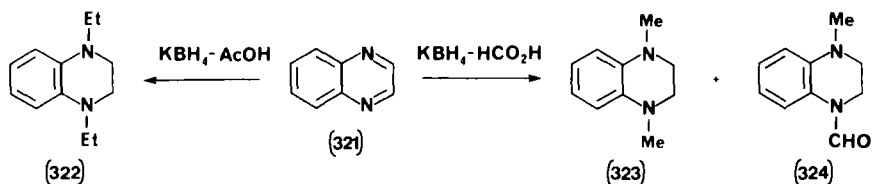
Monosubstituted 4-quinazolines, with the exception of the 1-¹⁶¹ and 3-phenyl¹⁵⁹ derivatives, do not undergo this ring opening reaction. The 2-phenyl derivative **319** leads to the product of carbonyl reduction **320** in 46% yield.¹⁶¹



The ring cleavage presumably occurs via the dihydro derivative; earlier work¹⁶⁵ had shown this ring opening to be facilitated when the reduction is carried out on the dihydro derivative. Failure of the carbonyl function to be reduced may be a result of the formation of a complex between it and the metal of the hydride reagent.

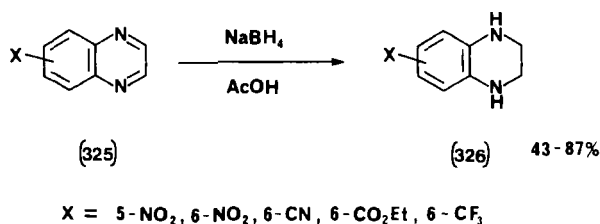
J. QUINOXALINES

Quinoxaline (**321**) was reductively alkylated with potassium borohydride in acetic acid by the method of Gribble and co-workers to give 1,4-diethyl-1,2,3,4-tetrahydroquinoxaline (**322**).¹⁶⁶ The use of formic instead of acetic acid gave mixtures of **323** and **324**. Quinoxalines **325** containing electron-withdrawing groups on the benzene ring can be efficiently reduced to the 1,2,3,4-tetrahydroquinoxalines **326** in high yield with NBH.⁹¹ No substituent reduction is observed.

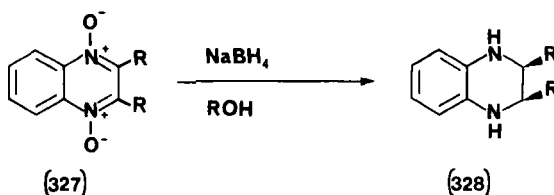


¹⁶⁵ K. Okumura, T. Oine, Y. Yamada, G. Hayashi, and M. Nakama, *J. Med. Chem.* **11**, 348 (1968).

¹⁶⁶ J. M. Cosmao, N. Collignon, and G. Queguiner, *J. Heterocycl. Chem.* **16**, 973 (1979).

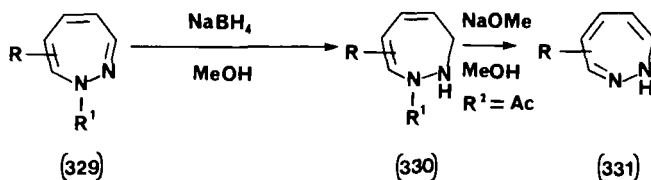


The NBH reduction of 1,4-quinoxaline di-*N*-oxide (327) in alcohols has been shown to produce the *cis*-tetrahydroquinoxalines 328 as the predominant product.¹⁶⁷ The product 328 was identical to that obtained from the reduction of 2,3-dimethylquinoxaline with LAH.¹⁶⁸



K. 1,2-DIAZEPINES

The NBH reduction of 1-acetyl- and 1-carbethoxy-1,2(1*H*)-diazepines (329) leads to the 2,3-dihydro-1,2(1*H*)-diazepines 330 in high yield.^{169,170} The dienamine system produced is resistant to further reduction under these conditions. That only single products were obtained was verified by preparing dihydro-1,2(1*H*)-diazepines labeled with methyl groups. Treatment of 330 ($R^1 = \text{Ac}$) with base generates the unstable 3,4-dihydro-1,2(2*H*)-diazepines 331. Analogous reduction is also observed with lithium disobutylaluminum hydride (DIBAL).¹⁶⁹



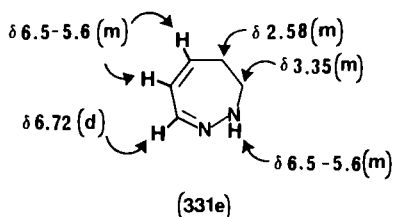
¹⁶⁷ M. J. Haddadin, H. N. Alkaysi, and S. E. Saheb, *Tetrahedron* **26**, 1115 (1970).

¹⁶⁸ J. Figueras, *J. Org. Chem.* **31**, 803 (1966).

¹⁶⁹ J. Streith and B. Willig, *Bull. Soc. Chim. Fr.*, 2847 (1973).

¹⁷⁰ T. Tsuchiya and V. Snieckus, *Can. J. Chem.* **53**, 519 (1975).

	a	b	c	d	e
R	H	3-Me	5-Me	4,6-di-Me	3,7-di-Me

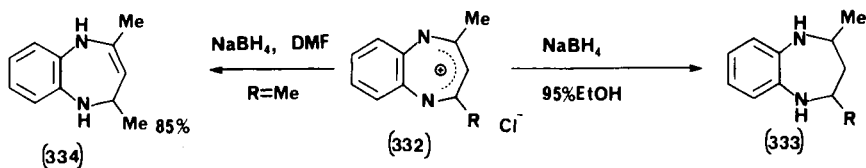


L. 1,4-DIAZEPINES

Most of the work on the 1,4-diazepines has been directed toward the reduction of oxo derivatives and other functionalities. These reactions will not be covered here, and interested readers are encouraged to refer to the appropriate sources.^{171,172}

M. 1,5-BENZODIAZEPINES

6,7-Benzo-1,2,4,5-tetrahydro-1,5-diazepines (333) may be obtained by the NBH reduction of the benzo-1,5-diazepinium chloride precursors 332. Yields in excess of 90% are claimed.¹⁷³ When the reduction was carried out in dimethylformamide, 2,4-dimethyl-1,5-dihydro-6,7-benzo-1,5-diazepine (334) was obtained. Additional work has shown that this reduction occurs stereoselectively, giving *cis*-tetrahydro-1,5-diazepines.¹⁷⁴



¹⁷¹ F. D. Popp and A. C. Noble, *Adv. Heterocycl. Chem.* **8**, 52 (1967).

¹⁷² D. Lloyd and H. P. Cleghorn, *Adv. Heterocycl. Chem.* **17**, 2 (1974).

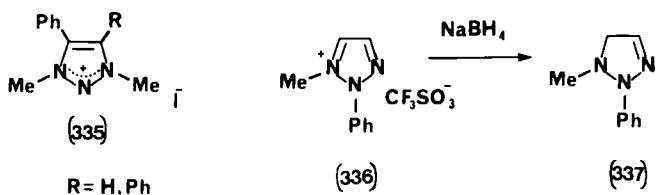
¹⁷³ N. M. Omar, *Indian J. Chem.* **12**, 498 (1974).

¹⁷⁴ N. M. Omar, A. F. Youssef, and M. A. El-Gendy, *Arch. Pharm. Chemi. Sci. Ed.* **3**, 89 (1975).

V. Reductions of Heterocycles Containing Three Nitrogen Atoms

A. 1,2,3-TRIAZOLES

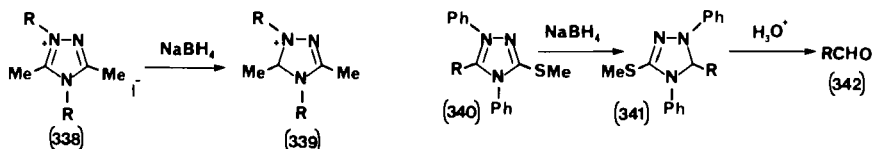
1,2,3-Triazolium salts (**335**) are not readily reduced by NBH_4 . Indeed, 4-phenyl- and 4,5-diphenyl-1,3-dimethyl-1,2,3-triazolium iodides do not undergo reduction, yet 1-methyl-2-phenyl-1,2,3-triazolium triflate (**336**) is reduced to the 4-triazoline **337**.¹⁷⁵ This reactivity pattern is explained by the need for an immonium ion for successful reaction. The presence of a C-2 substituent in **336** makes this possible; the lack of such a substituent localizes the double bond joining C-4 and C-5.



B. 1,2,4-TRIAZOLES

1,2,4-Triazolium salts (**338**) are readily reduced to the dihydro derivatives **339**, (triazolines) by aqueous NBH_4 . Similarly, borohydride attack occurs exclusively at the 5 position of 5-substituted-1,4-diphenyl-3-methylthio-1,2,4-triazolium salts (**340**) to give the triazolines **341** in high yield.¹⁷⁶ Acid hydrolysis of the triazolines leads to the aldehydes **342** in 40–80% yield.

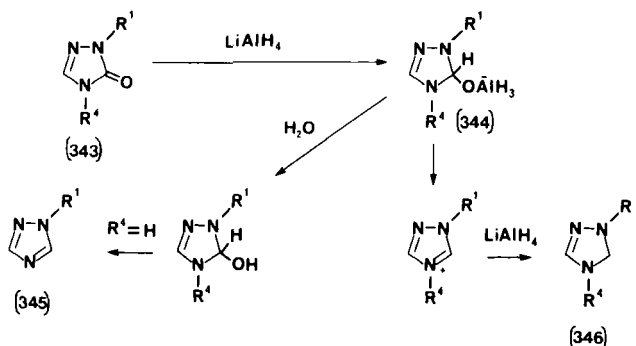
Lithium aluminum hydride has been used to convert the triazol-5-ones **343** to both triazoles (**345**) and triazolines (**346**). The yields of the former are low (15–30%) by this method, triazoline formation being preferred.¹⁷⁷



¹⁷⁵ T. Isida, T. Akiyama, N. Mihara, S. Kozima, and K. Sisido, *Bull. Chem. Soc. Jpn.* **46**, 1250 (1973).

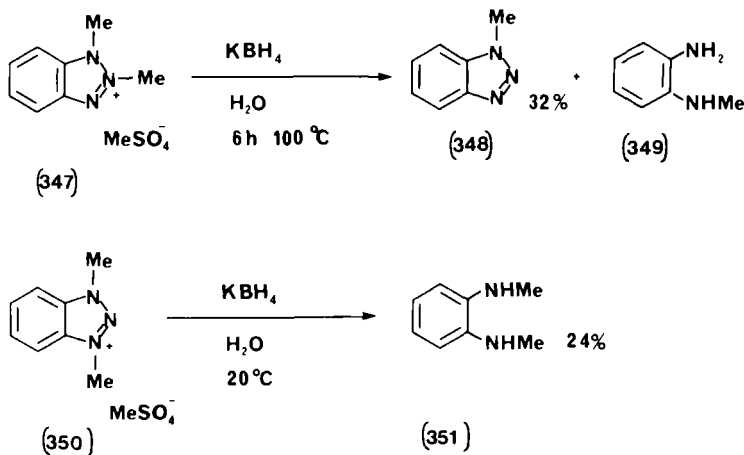
¹⁷⁶ G. Doleschall, *Tetrahedron* **32**, 2549 (1976).

¹⁷⁷ J. Daunis, Y. Guindo, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 3296 (1971).



C. BENZOTRIAZOLES

Attempts have been made to reduce 1,2- (347) and 1,3-benzotriazolium salts (350) both with potassium and sodium borohydride and LAH.^{175,178} The 1,2-dimethyl derivative yielded mainly 1-methylbenzotriazole (348) on heating with borohydride in water and probably results from base-controlled dealkylation. Small amounts of 349 were also detected. No reaction was observed in the cold with the iodides of 347 or 350.¹⁷⁵ 1,3-Dimethylbenzotriazolium methosulfate (350) gave 1,2-di(methylamino)benzene (351); heating at reflux produced intractable materials. The more reactive LAH, in ether, gave high yields of the ring-cleaved products 349 and 351, respectively.

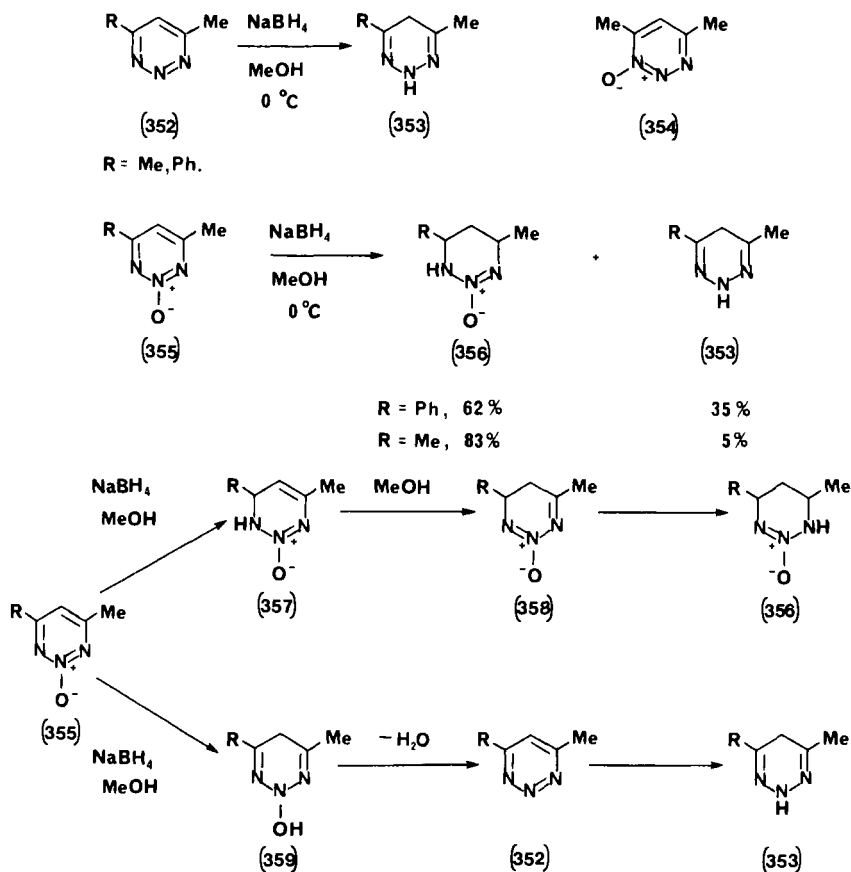


¹⁷⁸ L. I. Rudaya and A. V. El'tsov, *Zh. Org. Khim.* **10**, 2142 (1970).

D. 1,2,3-TRIAZINES

The electron-deficient triazine ring **352** is readily attacked by sodium borohydride in methanol to give the 2,5-dihydro-1,2,3-triazines **353** in quantitative yield.^{179,180} Under similar conditions 4,6-dimethyl-1,2,3-triazine 1-oxide (**354**) gave the same compound (**353**, R = Me) in 85% yield, along with **352** (R = Me).¹⁷⁹ However, reduction of the 1,2,3-triazine 2-oxides **355** left the *N*-oxide functionality intact for the most part, giving the 1,4,5,6-tetrahydro-1,2,3-triazine 2-oxides **356** as the major products.¹⁷⁹ Both *cis* and *trans* isomers of **356** were detected, the former predominating.

These results were confirmed by carrying out the reduction with sodium borodeuteride and deuteriomethanol. The C-5 proton originates from the



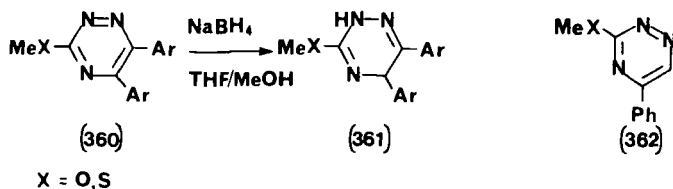
¹⁷⁹ H. Arai, A. Ohsawa, H. Ohnishi, and H. Igeta, *Heterocycles* **17**, 317 (1982).

¹⁸⁰ A. Ohsawa, H. Arai, H. Ohnishi, and H. Igeta, *J. C. S. Chem. Commun.* 1174 (1981).

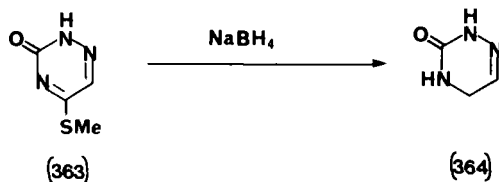
solvent whereas the C-4 and C-6 protons are from the reducing agent. The implication is that **356** arises from an initial 1,6-dihydrotriazine, whereas **353** forms from the 2,5-dihydro derivative **359**. The triazines **352** were detected in the product mixture.¹⁷⁹

E. 1,2,4-TRIAZINES

5,6-Diaryl-1,2,4-triazines (**360**), containing a 3-methoxy or 3-methylthio substituent, give rise to the formation of the 2,5-dihydro derivatives **361** on treatment with NaBH_4 .^{181,182} These dihydro species, trapped with dimethylacetylenedicarboxylate, were assigned structures by NMR spectroscopy, which were confirmed by X-ray analysis. 3-Methylthio- and 3-methoxy-5-phenyl-triazines (**362**) behaved similarly.¹⁸³ The 2,5- and 4,5-dihydro-1,2,4-triazines may be differentiated by NMR spectroscopy.¹⁸⁴ The 1,4-addition of hydrogen is explained by initial hydride attack at C-5 followed by N-2 protonation by the solvent.



A report on the reaction of NBH_4 with 5-methylthio-1,2,4-triazin-3(2H)-ones (**363**) claims demethiolation in methanol to 4,5-dihydro-1,2,4-triazin-3(2H)-ones (**364**) in good yield.¹⁸⁵ The same workers extended this study and described a similar reaction occurring on 3-methylthio-1,2,4-triazin-5(2H)-ones (**365**) in DMF at 70°C.¹⁸⁶ Conducting the reaction in methanol led to substantial amounts of **367** being isolated.



¹⁸¹ T. Sasaki, K. Minamoto, and K. Harada, *J. Org. Chem.* **45**, 4587 (1980).

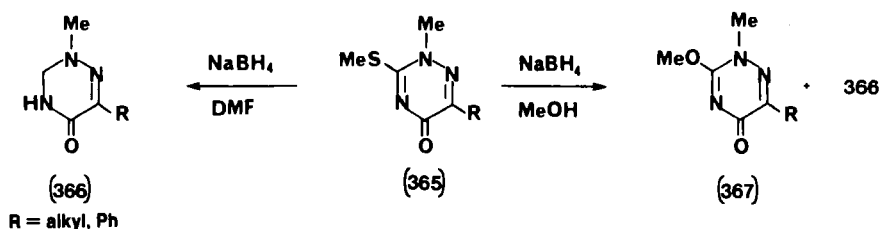
¹⁸² H. Neunhoeffer and P. F. Wiley, eds., "Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines and Pentazines." Wiley (Interscience), New York, 1978.

¹⁸³ T. Sasaki, K. Minamoto, and K. Harada, *J. Org. Chem.* **45**, 4594 (1980).

¹⁸⁴ J. Daunis and C. Pigiere, *Bull. Soc. Chim. Fr.*, 2493 (1973).

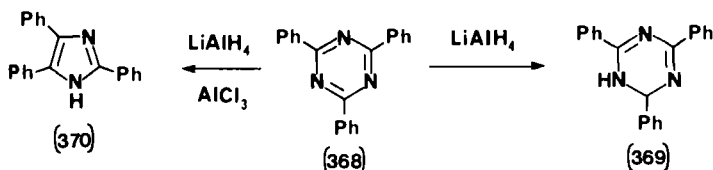
¹⁸⁵ Y. Nakayama, Y. Sanemitsu, M. Mizutani, and K. Yoshioka, *J. Heterocycl. Chem.* **18**, 631 (1981).

¹⁸⁶ Y. Sanemitsu, Y. Nakayama, and M. Shiroshta, *J. Heterocycl. Chem.* **18**, 1053 (1981).



F. 1,3,5-TRIAZINES

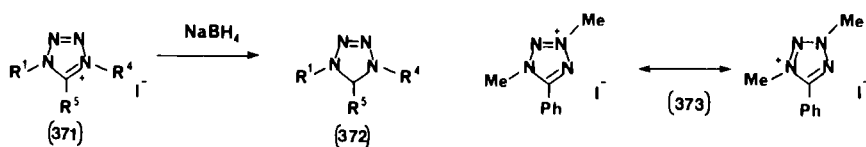
Studies on the stability of 1,2-dihydro-2,4,6-triphenyl-1,3,5-triazine (369) included its synthesis from the aromatic 1,3,5-triazine 368. However, in the presence of aluminum chloride rearrangement occurs to give a 16% yield of 2,4,5-triphenylimidazole (370).¹⁸⁷ A suggested mechanism proposed that the unstable dihydrotriazine undergoes a radical-induced ring opening and contraction to 370.¹⁸⁷



VI. Reduction of Heterocycles Containing Four Nitrogen Atoms

A. TETRAZOLES

The action of NBH on some tetrazolium iodides has been studied.¹⁷⁵ The positions of the substituents determined whether or not reduction occurred. 1,4,5-Trisubstituted tetrazolium iodides (371) were reduced to the 2-tetrazolines 372, whereas under the same conditions the 1,3,5-trisubstituted tetrazolium iodide 373 remained unchanged. The ring carbon is insufficiently electrophilic to induce attack.



¹⁸⁷ H. L. Nyquist, *J. Org. Chem.* **31**, 784 (1966).

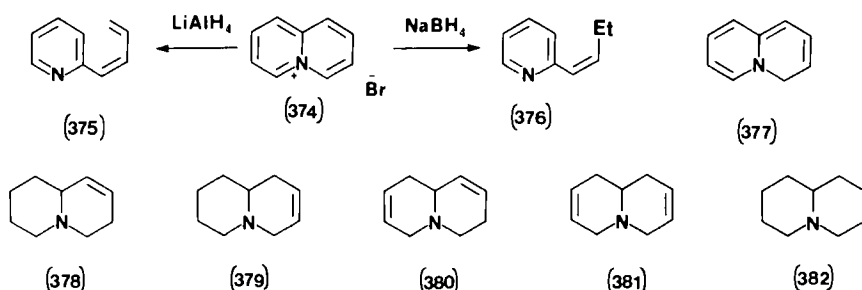
VII. Reduction of Fused Heterocycles

A. QUINOLIZINES

The reduction of quinolizinium bromide (**374**) with NBH and LAH has been the subject of a series of publications by Miyadera and coworkers.¹⁸⁸⁻¹⁹⁰ Hydride reduction with LAH (in THF) leads to ring cleavage to 1-(2-pyridyl)-1,3-butadiene (**375**), whereas NBH (in THF) gave 1-(2-pyridyl)-2-butene (**376**) in low yield.

Studies of the reaction of **374** with Grignard reagents^{190,191} and MO calculations¹⁹² indicate that the preferred site for nucleophilic attack of the quinolizinium ion is C-4. Thus the intermediacy of the unstable 4*H*-quinolizine **377**, formed directly or by isomerization, has been suggested. Reduction of **374** with NBH (1 : 1) in water gave a four-component mixture, which was shown by gas chromatography to contain the quinolizines **378-381**. Catalytic hydrogenation of the mixture gave quinolizidine (**392**). Conducting the reduction in deuterium oxide or deuterated ethanol led to incorporation of deuterium in the product.

The different products obtained in aprotic solvents reflects the possibility of ring opening and reestablishment of aromaticity to the pyridine ring. In water or ethanol the proposed intermediate **377** may undergo a variety of protonations and equilibrations prior to further reduction.¹⁸⁹ The reduction



of benzo[*b*]quinolizinium bromide (**383**) in ethanol with NBH led to the formation of 1,6,11,11a-tetrahydrobenzo[*b*]quinolizine (**384**) as the major product.¹⁹³ In boiling water, only the 1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine **386** was obtained.

¹⁸⁸ T. Miyadera and Y. Kishida, *Tetrahedron* **25**, 209 (1969).

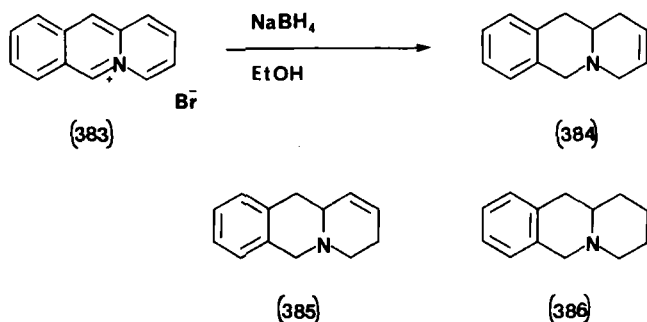
¹⁸⁹ T. Miyadera and Y. Kishida, *Tetrahedron* **25**, 397 (1969).

¹⁹⁰ T. Miyadera and Y. Kishida, *Tetrahedron Lett.*, 905 (1965).

¹⁹¹ C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.* **81**, 1938 (1959).

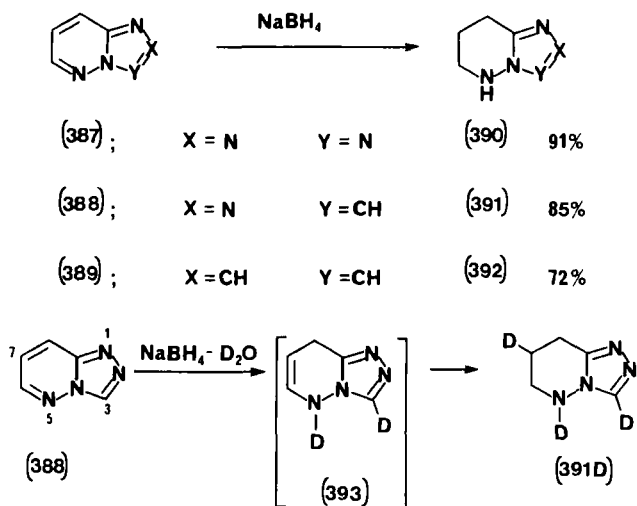
¹⁹² R. M. Acheson and D. M. Goodall, *J. Chem. Soc.*, 3225 (1964).

¹⁹³ T. Miyadera and R. Tachikawa, *Tetrahedron* **25**, 5189 (1969).



B. AZOLOPYRIDAZINES

The reduction of simple pyridazines normally occurs only after quaternization and leads to mixtures of di- and tetrahydropyridazines (see Section IV,E). However, bicyclic azolopyridazines containing a bridgehead nitrogen (387–389) readily undergo reduction of the pyridazine ring with NBH in ethanol.¹⁹⁴ Thus tetrazolo[1,5-*b*]- (387), 1,2,4-triazolo[4,3-*b*]- (388), and imidazolo[1,2-*b*]pyridazines (389) are reduced to the corresponding tetrahydro derivatives 390–392. The reduction of 388 in deuterium oxide led to deuterium incorporation at C-3, N-5, and C-7 in 391. Hydrogen–deuterium exchange will occur at C-3 in both 388 and 391 and at N-5 in 391. Deuterium incorporation at C-7 can be seen as occurring via the intermediate 393.¹⁹⁴

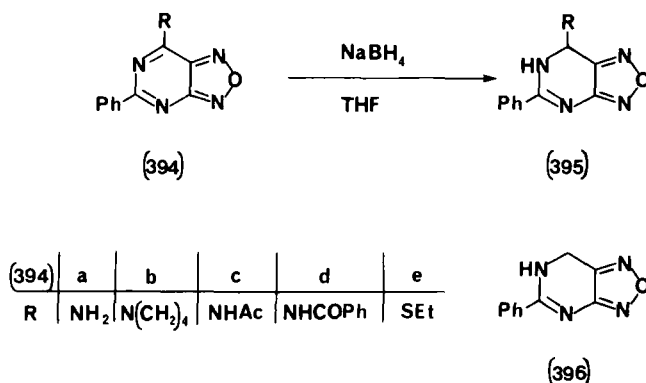


¹⁹⁴ P. K. Kadaba, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.* **13**, 835 (1976).

C. AZOLOPYRIMIDINES

1. 1,2,5-Oxadiazolo[3,4-d]pyrimidine

Previous work on this system by Taylor *et al.*¹⁹⁵ has illustrated the facile nucleophilic attack that occurs at C-7. Reduction of the 5-phenyl-7-substituted derivatives with NBH in THF has been shown to be substituent dependent.¹⁹⁶ Amino substituents (**394a**, **394b**) inhibit reduction, whereas the thioester **394e** gives the product of reductive cleavage **396**. The 6,7-dihydro derivative is obtained from the acetamido compound **394c**. However, the benzamido analog **394d** gives **396** and benzamide in 60% yield.



2. Imidazolo[4,5-d]pyrimidine

The purine ring system has been the subject of considerable study, which is a reflection of its biological importance. Reduction of the imidazole or pyrimidine ring is controlled by the nature and position of substituents; for instance, 1-methyladenosine (**397**) undergoes ready reduction with NBH to the 1,6-dihydro derivative **398**.¹⁹⁷ 9-Benzyladenine (**399a**) and its *N*-benzoyl derivative **399b** remained unchanged on treatment with NBH in alcohols.¹⁹⁸ Reduction of **399b** with NBH in acetic acid gave reduction in the imidazole ring to afford the 7,8-dihydro compound **400b**, (75%) but without the *N*-ethylation previously observed with this method. A similar reduction of the *N*-acetyl derivative has been observed, but the product was not isolated. The

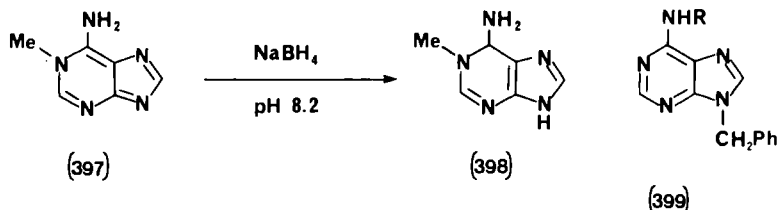
¹⁹⁵ E. C. Taylor, S. F. Martin, Y. Maki, and G. P. Beardsley, *J. Org. Chem.* **38**, 2238 (1973).

¹⁹⁶ Y. Maki, *Chem. Pharm. Bull.* **24**, 235 (1976).

¹⁹⁷ J. B. Bacon and R. Wolfenden, *Biochemistry* **7**, 3453 (1968).

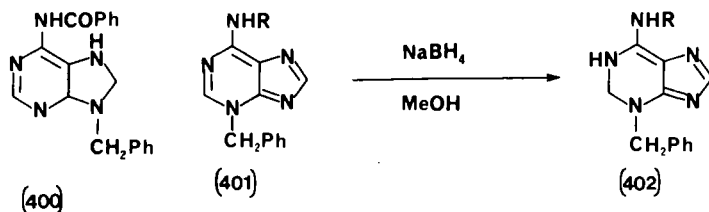
¹⁹⁸ Y. Maki, M. Suzuki, and K. Ozeki, *Tetrahedron Lett.*, 1199 (1976).

adenine **399a** was recovered unchanged under these conditions. Reductive sites were determined by deuterium labeling. The site of reduction appears to be the enamine system, which can generate an imminium ion in a protic solvent. 3-Benzyl derivatives (**401**) were used in order to confer the required



(399)	a	b
R =	H	COPh

stability to the dihydro derivatives **402**.¹⁹⁸ 3,9-Dimethyladeninium per-



(401)	a	b	c
R	H	COPh	Ac

chlorate (**403**) undergoes reduction with NBH in methanol to give the 2,3-dihydro compound **404**.¹⁹⁹

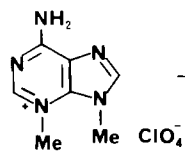
The purine derivatives **405** and **407** undergo reduction in the pyrimidinium and imidazolium rings, respectively.²⁰⁰ Studies on the reduction of 2,8-dioxo- and 2,8-diaminopurines were carried out in order to study the simpler chemical derivatives of saxitoxin.²⁰¹ Attempts to reduce 1,7-dihydro-9H-purine-2,8-dione (**409**) with NBH were unsuccessful.

Reduction of 3,7,8,9-tetrahydro-1,3,9-trimethyl-2,8-dioxo-2H-purinium iodide (**410**, R = H) under the same conditions gave spectral evidence for generation of the hexahydro derivative. However, on attempted isolation, facile hydrolytic C-4—C-9 ring cleavage occurred, and the uracil **411** (R =

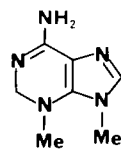
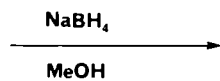
¹⁹⁹ T. Fujii, T. Saito, T. Nakasaka, and K. Kizu, *Heterocycles* **14**, 1729 (1980).

²⁰⁰ Z. Neiman, *J. Chem. Soc. C*, 91 (1970).

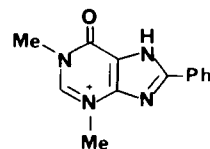
²⁰¹ W. L. F. Armarego and P. A. Reece, *J. C. S. Perkin I*, 1414 (1976).



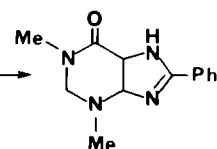
(403)



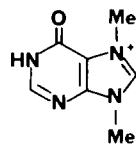
(404)



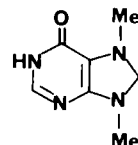
(405)



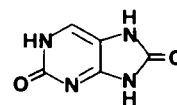
(406)



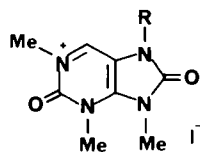
(407)



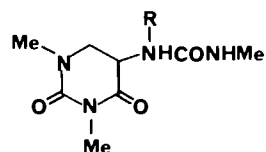
(408)



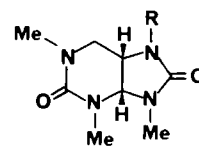
(409)



(410)



(411)

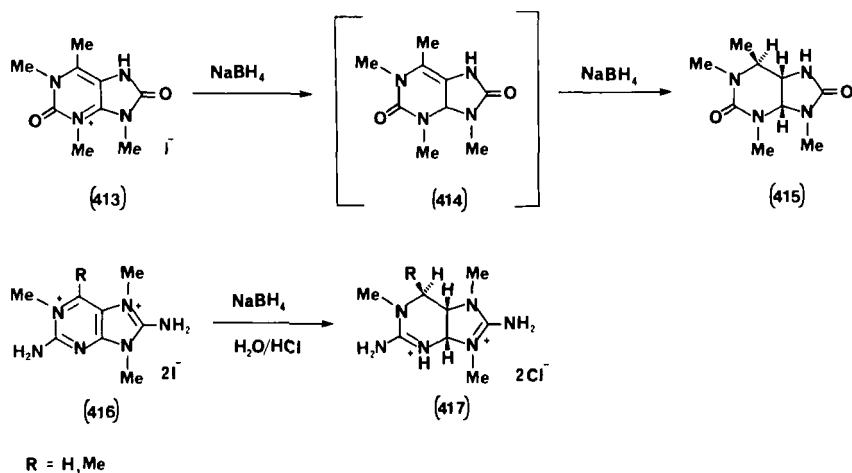


(412)

H) was produced. In methanol, at pH 9 and with excess NBH, the perhydro compound **412** ($R = H$) was formed in high yield. This was shown by 1H NMR to be the *cis* fused product.²⁰¹ Similarly, the reduction of the 1,3,7,9-tetramethyl derivative **410** ($R = CH_3$) provided the *cis* product **412** ($R = CH_3$).

In D_2O , NBH gave incorporation of a deuterium atom at C-5, suggesting that hydride attack occurs at C-4 in generating the hexahydro and at C-4 and C-6 in formation of the perhydro species. The reduction of 3,7,8,9-tetrahydro-1,3,6,9-tetramethyl-2,8-dioxo-2*H*-purinium iodide (**413**) with NBH proceeds more slowly to the perhydro derivative **415** but via a different hexahydro intermediate (**414**).

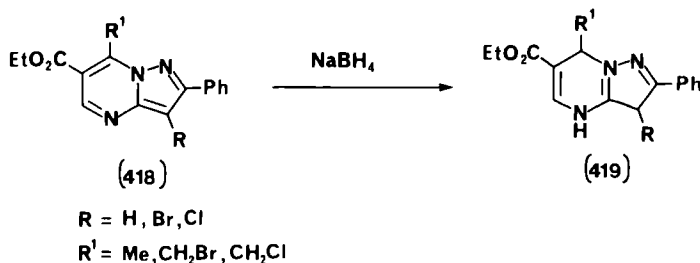
The reduction of 1,7,9-trimethyl-2,8-diaminopurinium diiodide (**416**, $R = H$) gave only one product with NBH, the 2,8-diamino-4,5,6,9-tetrahydro-1,7,9-trimethyl-1*H*-purine cation (**417**, $R = H$).²⁰¹ The 1,6,7,9-tetramethylpurine **416** ($R = Me$) similarly gave the tetrahydro product **417** ($R = Me$). Both of these products were isolated as the dihydrochlorides in high yield and contained a *cis*-ring junction.²⁰¹



3. *Pyrazolo[1,5-a]pyrimidine*

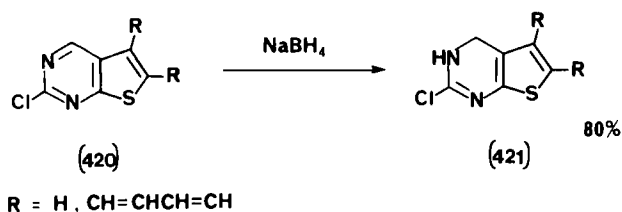
Ethyl 2-phenylpyrazolo[1,5-*a*]pyrimidinecarboxylates (**418**) are converted to the dihydro derivatives **419** on treatment with NBH.²⁰²

²⁰² G. Auzzi, L. Cecchi, A. Costanzo, P. L. Vettori, and F. Bruni, *Farmaco, Ed. Sci.* **34**, 751 (1979).



D. THIENO[2,3-*d*]PYRIMIDINE

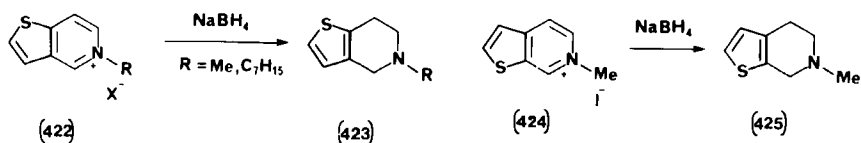
2-Chloro-3,4-dihydrothieno[2,3-*d*]pyrimidines (**421**) are prepared when the aromatic precursors **420** are treated with excess NBH_4 over an 8-h period at room temperature.²⁰³



E. THIENOPYRIDINES

1. Thieno[3,2-*c*]- and Thieno[2,3-*c*]pyridines

N-Alkylation and subsequent reduction of both thieno[3,2-*c*]- (**422**) and thieno[2,3-*c*]pyridines (**424**) give predictably the 4,5,6,7-tetrahydrothienopyridines **423** and **425**, respectively. Large excesses of borohydride were used, and the reductions were carried out in ethanol over 4-h periods at reflux temperatures. Yields of 57–78% are obtained.²⁰⁴ The relatively electron-rich thiophene ring resists reduction.



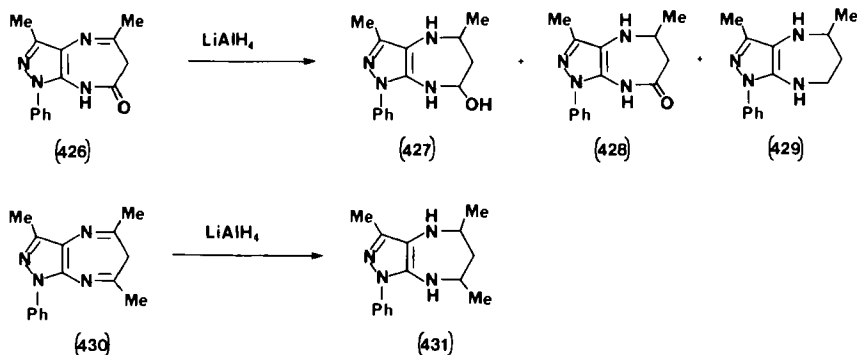
²⁰³ Daiichi Seiyaku Co., Ltd., *Jpn. Kokai Tokkyo Koho* **82/77,687** (1982).

²⁰⁴ F. Eloy and A. Deryckere, *Bull. Soc. Chim. Belg.* **79**, 415 (1970).

F. AZOLOAZEPINES

1. *Pyrazolo[3,4-*b*]-1,4-diazepine*

3,5-Dimethyl-7-oxo-1-phenyl-6,8-dihydro-7*H*-pyrazolo[3,4-*b*]-1,4-diazepine (**426**) gave a mixture of three products on reduction with LAH. After heating at reflux for 6 h in ether, the ratio of **427**:**428**:**429** was 5:4:8; after 24 h only **429** was found. Reduction of 1-phenyl-3,5,7-trimethylpyrazolo[3,4-*b*]-1,4-diazepine (**430**) under similar conditions led to the tetrahydro derivative **431**²⁰⁵ in 80% yield after 12 h. 7,8-Dihydro derivatives of **430** were isolated on catalytic hydrogenation and could be subsequently converted to **431** with LAH.²⁰⁵



G. AZANAPHTHALENES

1. *Pyrido[3,2-*e*]-and Pyrido[3,4-*e*]-1,2,4-triazines*

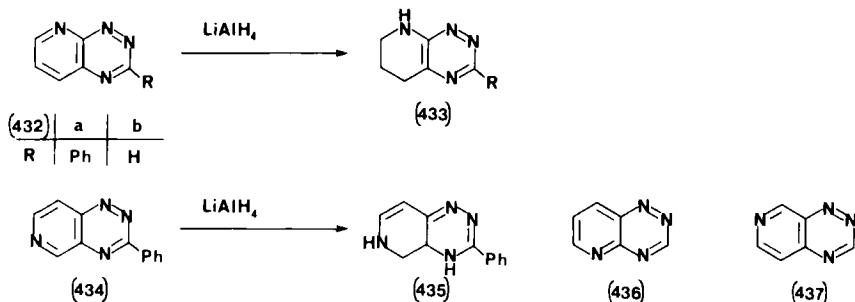
The addition of LAH to a solution of 3-phenylpyrido[3,2-*e*]-1,2,4-triazine (**432a**) in THF gave the tetrahydro derivative **433a**. Likewise with the unsubstituted analog **432b**, reduction occurred in the pyridine ring affording **433b**. 3-Phenylpyrido[3,4-*e*]-1,2,4-triazine (**434**), however, undergoes hydride reduction in both rings to give the 4,5,6,10-tetrahydro derivative **435**.²⁰⁶ The reason for this disparity is not obvious. Theoretical studies do not resolve the issue. One study indicates that in pyrido-1,2,4-triazines and pyridopyridazines the pyridine-ring nitrogen is the most basic.²⁰⁷ However,

²⁰⁵ J.-P. Affane-Nguema, J.-P. Lavergne, and P. Viallefont, *J. Heterocycl. Chem.* **14**, 1013 (1977).

²⁰⁶ J. Armand, K. Chekir, N. Ple, G. Queguiner, and M. P. Simonnin, *J. Org. Chem.* **45**, 4754 (1981).

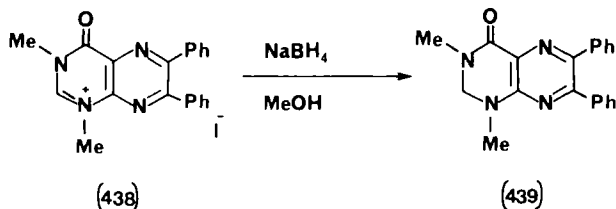
²⁰⁷ S. C. Wait, Jr. and J. W. Wesley, *J. Mol. Spectrosc.* **19**, 25 (1966).

Dinya²⁰⁸ in a CNDO study concluded that this is not so in every case. The pyridine N atom in pyrido[2,3-*e*]- (436) and pyrido[3,2-*e*]-1,2,4-triazines (432) carries the largest negative charge and indicates that reduction should occur in the triazine ring for the [3,4-*e*] (434) and [4,3-*e*] (437) analogs. Previous work on other azanaphthalene systems suggests that reduction should occur in the triazine ring.



2. Pyrazino[2,3-*d*]pyrimidine

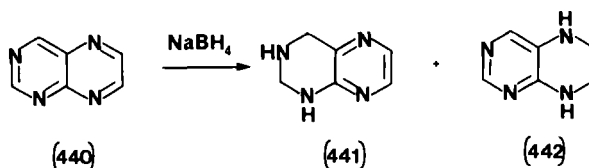
The reduction of pyrazine[2,3-*d*]pyrimidines, the pteridine ring system, usually occurs in the pyrazine ring to yield dihydro and tetrahydro derivatives.²⁰⁹ The reduction of 1- and 3-methyl-6,7-diphenylpteridin-4-one with NBH gives no isolable products, whereas 3,4-dihydro-1,3-dimethyl-6,7-diphenyl-4-oxopteridin-ium iodide (438) gives the 1,2,3,4-tetrahydro product 439.²⁰⁰ The reduction of pteridine (440) itself with NBH occurs readily in trifluoroacetic acid, giving two products in 94% overall yield. 1,2,3,4-(441) and 5,6,7,8-tetrahydropteridine (442) were obtained in 38 and 58% yields, respectively.²¹⁰ The pyrazine ring is preferentially reduced.



²⁰⁸ Z. Dinya and P. Benko, *Acta Chim. Acad. Sci. Hung.* **96**, 61 (1978).

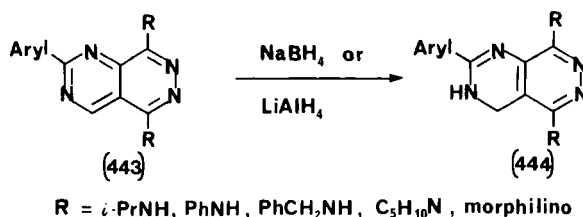
²⁰⁹ E. C. Taylor, M. J. Thompson, and W. Pfeider, *Pteridine Chem., Proc. Int. Symp., 3rd*, 1962, 181 (1964).

²¹⁰ R. C. Bugle and R. A. Osteryoung, *J. Org. Chem.* **44**, 1719 (1979).



3. Pyrimidino[4,5-*d*]pyridazine

Reduction of 2-aryl-5,8-dialkylaminepyrimido[4,5-*d*]pyridazines (**443**) with NBH_3 , LAH, and catalytic hydrogenation gives the 3,4-dihydropyrimido[4,5-*d*]pyridazines **444**.²¹¹



4. Pyrido[3,4-*d*]pyrimidine

The expected product of reduction of the pyrido[3,4-*d*]pyrimidin-4(3*H*)-one **445** with LAH is the 1,2,3,4-tetrahydropyrido[3,4-*d*]pyrimidine **446**. However, the product obtained (**447**) resulted from cleavage at the 2,3 position.²¹² High yields of the pyridine **447** were obtained after 1-h at room temperature with excess LAH. Reductive ring closures of fused pyrimidines and pyrimidin-4(3*H*)-ones has been reported previously to occur at the 1,2²¹³ and the 2,3 bond²¹⁴ (see also Section IV,F) but under much more vigorous conditions. More vigorous conditions are required when the pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones do not possess a 3-aryl substituent. The substrate **448** required 3 days at room temperature to give 1,2,3,4-tetrahydro-3,6,8-trimethylpyrido[3,4-*d*]pyrimidine (**449**) in 92% yield. Heating the pyridopyrimidone **448** at reflux in THF for 6 h was required to convert this to the pyridine **450**.²¹² Compounds without 3 substituents led to specific

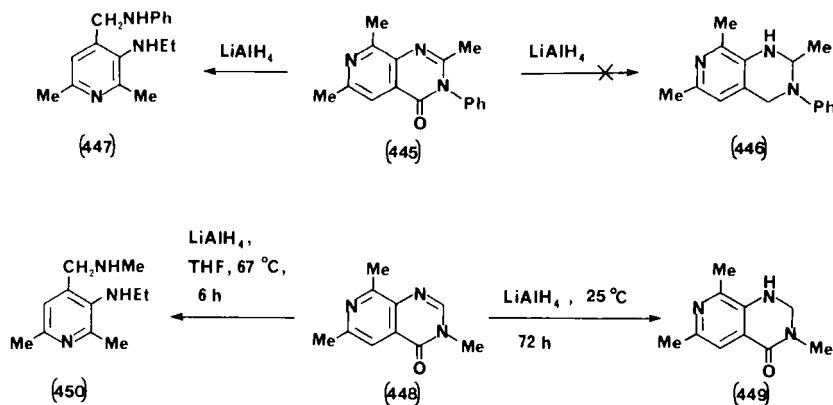
²¹¹ S. Yurugi, T. Fushimi, and M. Hieda, *Yakugaku Zasshi* **92**, 1316 (1972).

²¹² I. R. Gelling and D. G. Wibberley, *J. Chem. Soc. C*, 780 (1971).

²¹³ R. F. Smith, P. C. Briggs, R. A. Kent, J. A. Albright, and E. J. Walsh, *J. Heterocycl. Chem.* **2**, 157 (1965).

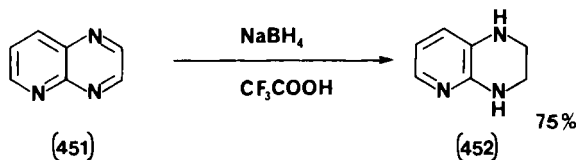
²¹⁴ H. Ott and M. Denzer, *J. Org. Chem.* **33**, 4263 (1968).

2,3-bond fission but with more difficulty (boiling ether, 7 days). Use of less reducing agent and lower temperatures gave mixtures of products, starting materials, and 3,4-dihydro derivatives. The latter are likely intermediates in the reduction, although initial 1,2 attack has also been suggested.^{160,165,214}



5. *Pyrido[2,3-*b*]pyrazine*

Pyrido[2,3-*b*]pyrazine (451) is reduced rapidly and regiospecifically by NBH in trifluoroacetic acid to the 1,2,3,4-tetrahydropyrazine 452.²¹⁰ No reduction of the pyridine ring was observed. Reduction with LAH on this and pyrido[3,4-*b*]pyrazines leads to tetrahydropyrazines.²⁰⁶

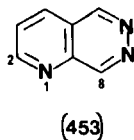


6. *Pyrido[2,3-*d*]pyridazine*

Calculations of the π -electron density²¹⁵ of pyrido[2,3-*d*]pyridazine (453) suggests that the nucleophilic attack is favored at C-2, C-5, and C-8. Studies of the reaction of 453 with LAH in THF gave 5,6- and 7,8-dihydro compounds in 35 : 65 ratio and 75% overall yield. The preferred site of attack is at

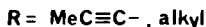
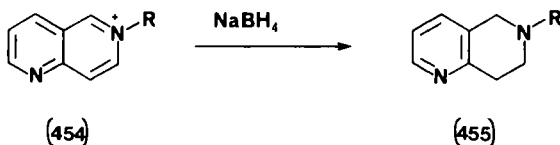
²¹⁵ M. Tisler and B. Stanovnich, "The Chemistry of Heterocyclic Compounds," Vol. 27, p. 989. Wiley (Interscience), New York, 1973.

C-8 as a result of the greater deactivation of the pyridazine ring and the proximity of the pyridine nitrogen.²¹⁶



7. *Pyrido[4,3-b]pyridine*

The tetrahydro derivatives **455** are conveniently prepared in aqueous methanol, using NBH.²¹⁷ Quaternization of the parent heterocycle gives the precursor **454**.



H. AZOLOINDOLES

1. *Pyrido[2,3-b]-, -[3,4-b]-, and -[4,3-b]indoles*

The reduction of the 1,2,3,4-tetrahydropyrido[4,3-*b*]indolinium salts (**456**) proceeds stereospecifically with NBH to give the trans-ring junction (**457**).²¹⁸ Pyridine-borane yields the *cis* product. A deep orange color is generated from the pyrido[3,4-*b*]indolinium salt **458** on treatment with NBH. This suggests the formation of the anhydro base **459** ($R = \text{H}$), the color of which dissipates as the 1,2,3,4-tetrahydro derivative **460** is formed.²¹⁹ The pyrido[2,3-*b*]indole **461** ($R = -$) is reportedly not affected by NBH. The salt **461** ($R = \text{CH}_3 +$) is, however, reduced.²²⁰

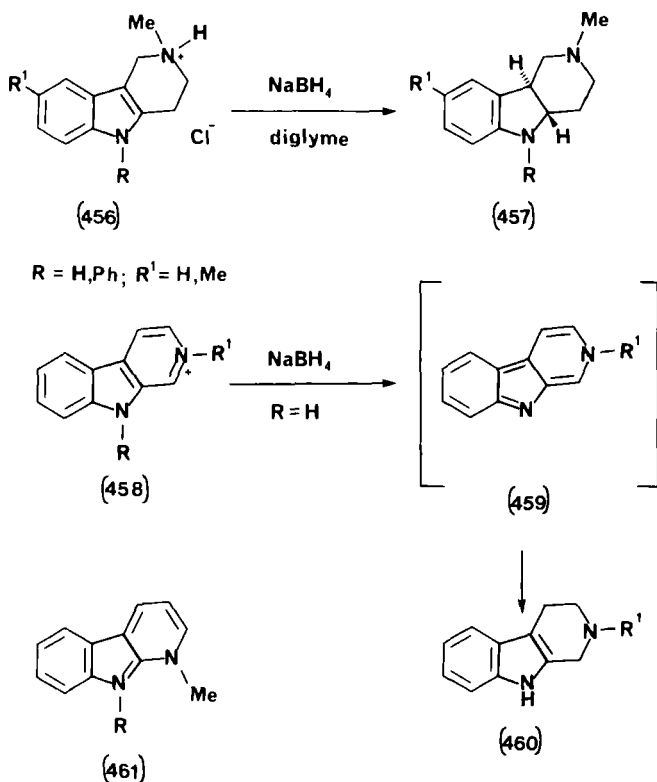
²¹⁶ D. Marchand, A. Turck, G. Queguiner, and P. Pastour, *Bull. Soc. Chim. Fr.* 919 (1977).

²¹⁷ Nippon Kayaku Co., Ltd., *Jpn. Kokai Tokkyo Koho* **81 135,848** (1980).

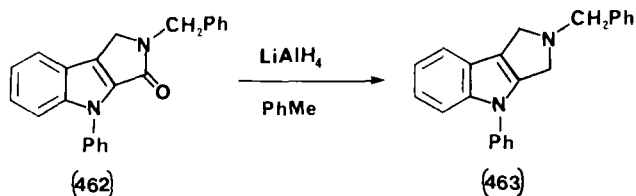
²¹⁸ V. A. Zagorevskii, S. G. Rozenberg, N. M. Sipilina, L. U. Bykova, and A. P. Rodiono, *Zh. Vses. Khim. O-va* **27**, 102 (1982).

²¹⁹ I. W. Elliott, *J. Heterocycl. Chem.* **3**, 361 (1966).

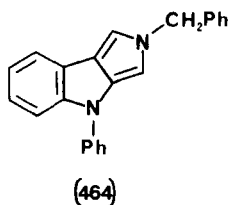
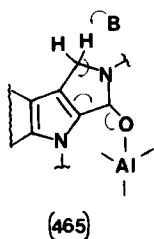
²²⁰ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **75**, 4475 (1953).



The reduction of the pyrrolo[3,4-*b*]indol-3(2*H*)-ones **462** with LAH in toluene at reflux temperatures gave the expected 1,2,3,4-tetrahydro derivative **463** in 45% yield. However, the dihydropyrrolo[3,4-*b*]indole **464** was also isolated. The yield of this latter product was increased from 27 to 42% when the reduction was carried out in the presence of 1-ethylpiperidine.²²¹ This was interpreted as increasing the propensity toward C-1 proton extrac-tion from the aluminum-oxygen complex **465**.

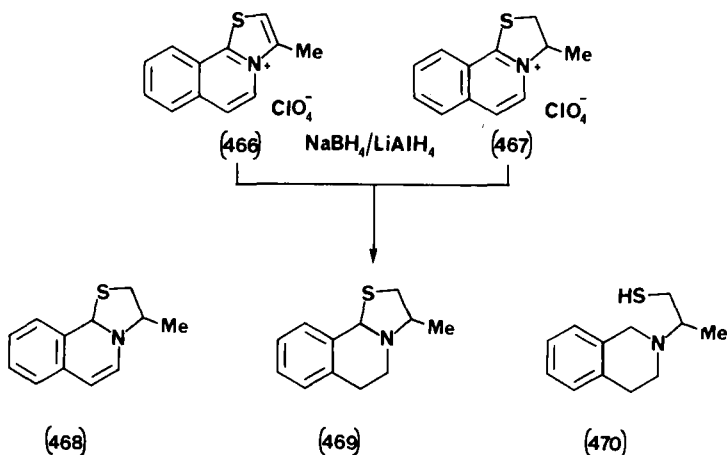


²²¹ W. M. Welch, *J. Org. Chem.* **41**, 2031 (1976).



I. 1,3-THIAZOLO[2,3-*a*]ISOQUINOLINE

The reduction of 3-methylthiazolo[2,3-*a*]isoquinolinium perchlorate (**466**) and its 2,3-dihydro derivative (**467**) led to the same three products with both NBH and LAH.²²² The formation of **469** was favored with borohydride, whereas **468** and **470** were the major product with LAH. Reductive ring cleavage of thiazoles is known and has been reported previously.²²³



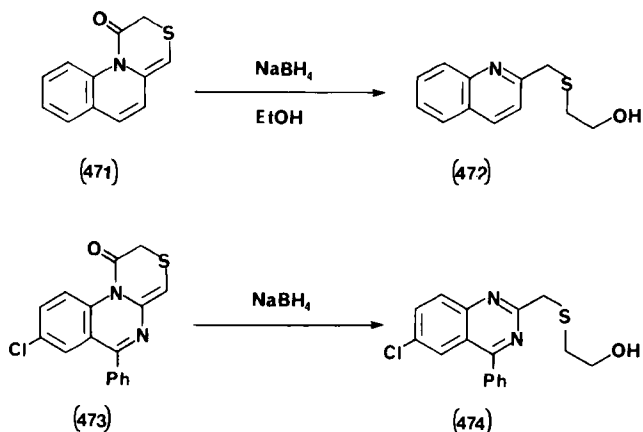
J. 1,4-THIAZENO[4,5-*a*]QUINOLINE AND -[4,5-*a*]QUINAZOLINE

Reduction with NBH leads to cleavage of the thiazine ring of **471** and produces the quinoline derivative **472**. The driving force for such a reaction

²²² H. Singh and K. Lal, *J. C. S. Perkin I*, 1799 (1972).

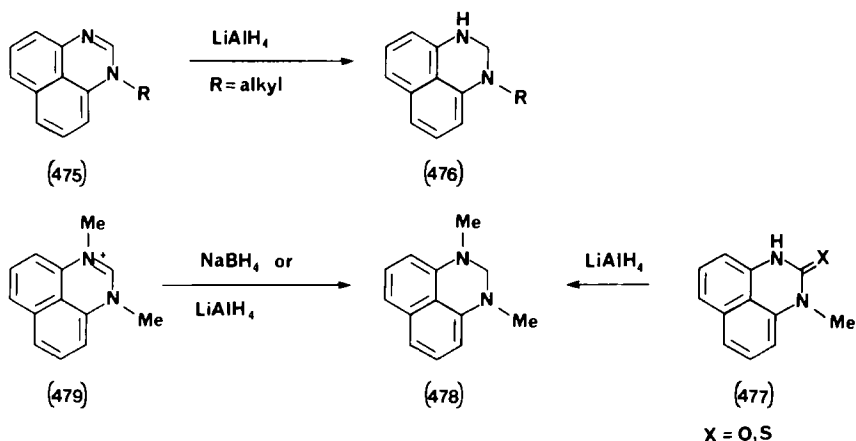
²²³ A. D. Clarke and P. Sykes, *J. Chem. Soc. C*, 103 (1971).

is rearomatization of the pyridine ring.²²⁴ Likewise, NBH in ethanol at reflux converts the thiazenoquinazoline **473** to the quinazoline **474**.²²⁴



K. BENZO[*d,e*]QUINAZOLINE

1-Substituted benzo[*d,e*]quinazolines (**475**, the perimidine ring system) are unaffected by NBH but are readily reduced to the 2,3-dihydro derivatives with LAH, yielding the 2,3-dihydroperimidines **476**. The perimidones and thiones **477** are readily reduced to **478** on treatment with LAH.²²⁵ The



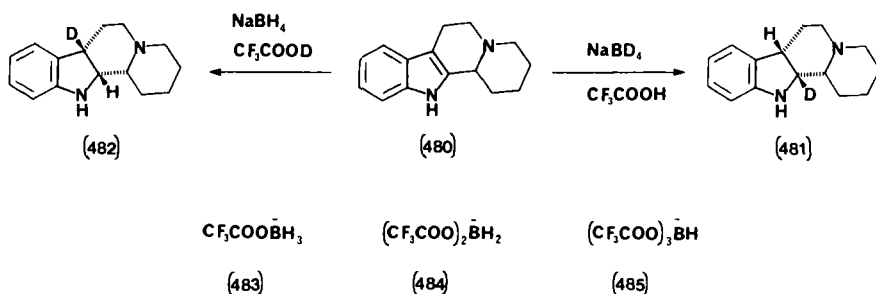
²²⁴ P. Neelakantan, N. Rao, U.T. Bhalarao, and G. Thyagarajan, *Indian J. Chem.* **11**, 1051 (1973).

²²⁵ A. F. Pozharskii and I. S. Kashparov, *Khim. Geterotsikl. Soedin.* **2**, 860 (1972).

1,3-substituted quaternary salts **479** undergo facile reduction to **478** with both of the above metal hydrides.²²⁶

L. INDOLO[2,3-*a*]QUINOLIZINE

Using NBH in trifluoroacetic acid has been shown to possess great utility for the reduction of indoles to indolines.¹⁰⁶ This ability has also been applied to the reduction of indole alkaloids.^{227,228} Studies on the alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**480**) gave the 1,2,3,4,6,7,7a,12,12a,12b-decahydro derivative **481**.²²⁹ Preparation of the deuterated derivatives enabled the stereochemistry of the ring junction to be determined as *cis* from the coupling constants observed in the undeuterated sample. This is in agreement with the proposed intermediacy of a bis- or tris(trifluoroacetoxy)borohydride species (**484**, **485**). These have a greater steric requirement than the monoacetate **483**, which is generated when the reaction is conducted in THF,²³⁰ giving a 20% yield of **481** along with a number of other stereo isomers (i.e., **482**).



M. PYRIDO[3,2,1-*k,l*]PHENOTHIAZINES

The reduction of the pyridophenothiazinium salts **486** in aprotic solvents leads to the 1,2-dihydro compounds **487**, which are relatively unstable. In

²²⁶ V. I. Sokolov, A. F. Pozharskii, I. S. Kashparov, A. G. Ivanov, and B. I. Ardashev, *Khim. Geterotsikl. Soedin.* **4**, 558 (1974).

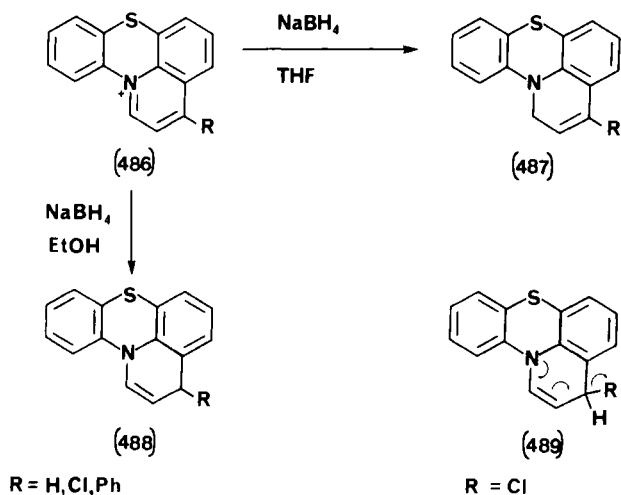
²²⁷ D. Herlem and F. K-Huu, *Tetrahedron* **35**, 633 (1979).

²²⁸ J. Le Men, L. Le Men-oliver, J. Levy, and M. C. Levy-Appert-Colin, German Patent 2,410,651 [*CA* **82**, 43640u (1975)].

²²⁹ G. W. Gribble, J. L. Johnson, and M. G. Saulnier, *Heterocycles* **16**, 2109 (1981).

²³⁰ G. W. Gribble, W. J. Kelly, and S. E. Emery, *Synthesis*, 763 (1978).

protic solvents with NBH the tetrahydro derivative **488** is formed.²³¹ Reduction of the 3-chloro derivative **486**, ($R = Cl$) gave the products **487** ($R = H$) and **488** ($R = H$) when conducted in different solvents. This probably results from the formation of the dihydro intermediate **489** ($R = Cl$), which rearomatizes with expulsion of the halogen. The reduction then continues as before.



ACKNOWLEDGMENTS

The author is most grateful to Dr. Eric F. V. Scriven for his continuous advice and support during the preparation of this manuscript. Dr. Robert E. Lyle generously supplied many references and undertook the reading of an early draft. Mr. Don Galow assisted with electronic data retrieval and the task of typing the manuscript was completed by Ms. Anita Brown.

Indulgence by Reilly Tar & Chemical Corporation is deeply appreciated, along with that of my colleagues, in particular, Ms. Cheryl Huss. A debt of gratitude is also due my wife, Debi.

The author remains solely responsible for errors and omissions.

²³¹ A. R. Martin, S. H. Kim, G. W. Peng, G. V. Siegel, and T. J. Yale, *J. Heterocycl. Chem.* **15**, 1331 (1978).

This Page Intentionally Left Blank

Mass Spectrometry of Nucleic Acids*

KRZYSZTOF JANKOWSKI

*Département de Chimie, Université de Moncton, Moncton, New Brunswick,
Canada E1A 3E9*

J. R. JOCELYN PARÉ

*Chemistry and Biology Research Institute, Agriculture Canada, Ottawa,
Ontario, Canada K1A 0C6*

ROBERT H. WIGHTMAN

*Department of Chemistry, Carleton University, Ottawa, Ontario, Canada
K1S 5B6*

I. Introduction	79
II. Bases	82
III. Nucleosides	85
IV. Nucleotides	91
V. Nucleic Acids and Polynucleotides	95
VI. Sequence of Ribo- and Deoxyribonucleotides and Nucleic Acids	106
VII. Concluding Remarks	112
VIII. Addendum	113
A. Mechanism of Py-MS of Oligonucleotides	113
B. Sequence Analysis	115

I. Introduction

At one time the idea of recording a mass spectrum of a nucleic acid would have been considered utopic and futuristic. Nucleic acids are practically nonvolatile and usually possess a molecular weight of several million atomic mass units (amu) (μ) often expressed in daltons: up to 10^9 daltons where 1 dalton = 1.67×10^{-24} g. They possess their own mass spectra. In general they are esters of phosphoric acid and polyols, such as the sugars ribose and 2'-deoxyribose, which are themselves substituted with heteroaromatic purine or pyrimidine bases. Consequently, fragment ions characteristic of all these structural elements can be found in the mass spectra of nucleic acids.

* C. B. R. I. Contribution No. 1538.

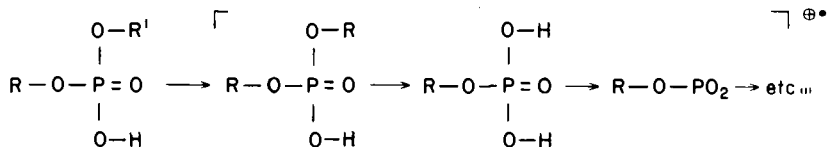


FIG. 1.

Phosphate esters show important thermal susceptibility (Fig. 1).¹ Dialkyl phosphates, such as those found in nucleic acids (Fig. 2), decompose with the initial loss of one alkyl group, the concomitant transfer of protons, followed by the elimination of the second alkyl group and the subsequent loss of water.¹ This thermal instability of phosphoesters has been used in the analysis of nucleic acids. Thus the pyrolysis that usually precedes the recording of a mass spectrum permits cleavage of the polymeric phosphoesters (nucleic acids), followed by phosphate extrusions, producing nucleotides or simple nucleosides as fragment ions.

The sugar components of DNA- and RNA-based nucleic acids participate in the formation of nucleoside subunits and under pyrolytic conditions will lead to a specific 2-methylfuran (**1a**) residue. RNA-based nucleic acids will also exhibit fragment ions due to 2-methyl-4-hydroxyfuran (**1b**) (Fig. 3). This behavior is typical of ribose derivatives. However, the attachment of the fragments **1a** or **1b** to other ions formed in the fragmentation processes is unusual. The **1a** unit, for example, undergoes dimerization, and ions con-

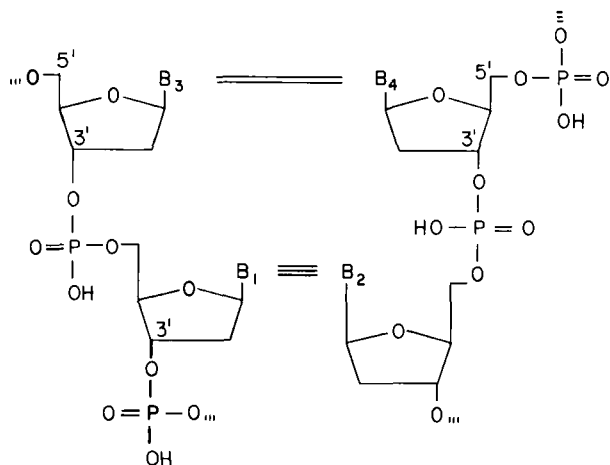
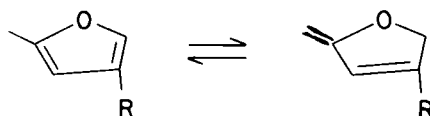


FIG. 2. DNA of similar polarity.

¹ H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," pp. 28-42. Holden-Day, San Francisco, California, 1967.



1a for DNA R = H
1b for RNA R = OH (OR')

FIG. 3.

taining one or two units of **1a** are observed in the mass spectrum of DNA recorded under pyrolytic conditions. The nature of the bonds involved in such aggregates is not known. It is reasonable to believe that they result from the dimerization of two furan tautomers; a similar reaction, acid catalyzed, occurs at normal pressure producing a trimer rather than a dimer² (Fig. 4).

Finally, the heterocyclic base moieties on the nucleic acids, so important in the formation of hydrogen bonding and responsible for their essential functions, display a fairly predictable behavior under mass spectrometric conditions. Under normal electron impact (EI) conditions, these bases show a good stability related to a favored delocalization of the unpaired electrons. Because of this high stability of the species involved, ions due to base units are the most characteristic fragments obtained from the complex spectra of nucleic acids. Another interesting feature is the tautomeric modification of bases that is responsible for the S_E or S_N type quenching of the reagent gas when the applied chemical ionization (CI) conditions involve negative or positive ions, respectively.

The sequencing of nucleic acids remains one of the most challenging applications of mass spectrometry. New technological developments centered around the ionization process have brought an unexpectedly quick answer to this problem. Although species with molecular masses of several million daltons can not yet be handled, the sequencing of shorter polynucleotides is easily done, using the technique of fast atom bombardment



FIG. 4.

² L. F. Fieser, "Topics in Organic Chemistry," p. 64. Van Nostrand-Reinhold, Princeton, New Jersey, 1963; also see L. Paquette, "Modern Heterocyclic Chemistry," p. 105. Benjamin, New York, 1968.

(FAB) coupled to a data system to simplify the task of analyzing the complex FAB spectra. This is the latest and certainly the most active research area in "state-of-the-art" mass spectrometry of nucleic acids. There is little doubt that this positive response to the challenge involved in the sequencing of nucleic acids should allow mass spectrometry to occupy a select position among modern analytical techniques.

II. Bases

Because of the abundance of their molecular ions, pyrimidine and purine bases of DNA or RNA are easily detected (e.g., after thermolysis). Both families of aromatic bases have been extensively investigated and their fragmentation pathways have been reviewed by McCloskey³ and Higgins.^{4,5} The fragmentation process, as established by metastable ion studies, high resolution mass measurements, and various labeling and derivatization experiments, has shown that base ions (more particularly $[BH]^+$, a protonated base) are an invaluable identification tool for nucleic acids. In this review the bases have been divided into two groups according to their origin: DNA (Table I)⁶ and RNA (Table II), with a distinction being made between normal and modified.

Typical fragmentation of both types of base involves the loss of small neutral molecules such as HCN, CO, and CH_3CN , as well as some extensive rearrangements in aromatic compounds. The most common derivatization, silylation under normal conditions (TMSC, HMDS/TMSC, BSA, or BSTFA/TMSC, ∇ , 20 min–2 hr), with or without pyridine as a solvent and base catalyst, usually leads to the enolic forms of the bases via the corresponding silyl ether. The persilylated derivatives are volatile enough to be used in gas chromatography–mass spectrometry (GC–MS). This enhancement of volatility compared to that of the free bases is the key factor making GC–MS a widely used analytical method in this area.

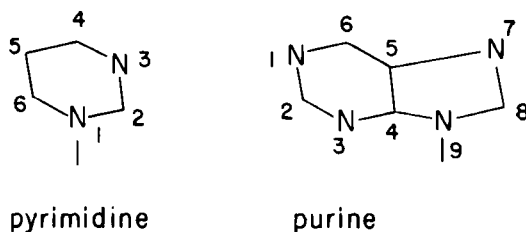
One of the newest silylation agents, *t*-butyldimethylsilyl chloride (TBMSCl), offers no particular advantage in base silylation. However, be-

³ J. A. McCloskey, in "Basic Principles in Nucleic Acid Chemistry" (P.O.P. Ts'o, ed.), Vol. 1, Chapter 3, pp. 209–309. Academic Press, New York, 1974.

⁴ C. Higgins, in "Biochemical Applications of Mass Spectrometry" (G. R. Waller, ed.), Chapter 16, pp. 429–443. Wiley (Interscience), New York, 1970.

⁵ C. Higgins, in "Biochemical Applications of Mass Spectrometry" (G. R. Waller and O. C. Dermer, eds.), 1st Suppl. Vol., Chapter 16, pp. 527–566. Wiley (Interscience), New York, 1980.

⁶ J. L. Wiebers, *Nucleic Acids Res.* **3**, 2959 (1976).

TABLE I
MAJOR DNA BASES

skeletons

Normal		Modified	
Pyrimidine	Purine	Pyrimidine	Purine
Thymine (T)	Adenine (A)	5-Hydroxymethyluracil (HMU)	6-Methylamino-purine (HMA)
Cytosine (C)	Guanine (G)	5-Methylcytosine (5MC) Hydroxymethylcytosine (HMC) 5-Carboxymethyl-deoxyuracil (5CMU) ^a 5-(4',5'-Dihydropentyl)deoxyuracil (5DHPU) ^a	1-Methyladenine (MA)

^a From modified DNA.⁶TABLE II
MAJOR RNA BASES

Normal		Modified	
Pyrimidine	Purine	Pyrimidine	Purine
Uracil (U)	Adenine (A)	5-Methylcytosine (5MC)	N(6)-Dimethyladenine (DMA)
Cytosine (C)	Guanine (G)	N(6)-Acrylcytosine (NAC)	1-Methyladenine (MA)
		2'-O-Methylcytosine (OMC)	N(6)-Isopentyladenine (NPA)
		4,5-Dihydrouracil (DHU)	N(2)-Dimethylguanine (DMG)
		2'-O-Methyluracil (OMU) ^a	N(2)-Methylguanine (NMG)
			1-Methylguanine (1MG)
			N(7)-Methylguanine (7MG)
			Inosine (hypoxanthine or 6-hydroxypurine) I
			1-Methylinosine (MI)

^a Also note pseudouridine (PSU), ribothymidine (RT).

cause of its selectivity toward the 5'-hydroxy sugar, it is in common use for nucleosides.⁷⁻⁹

Chemical modifications in the structure of nucleic acids often occur at the base level. The resulting "modified bases" and their detection is then of extreme importance to biochemists. Monitoring the action of chemotherapeutics is often accomplished by looking at base fragments. Similarly, the results of various illnesses can be assessed by the detection of given modified bases. Mass spectra of silylated cytosine and one of the minor bases in mammalian DNA, 5-methylcytosine, have been used as a tool for determining the ratio of these two bases from hydrolysates of nucleic acids.¹⁰ The intensities of the molecular ions of both disilylated bases (m/z 269/240) have also been used for the preparation of semiempirical curves that enable the detection of up to 1.6 pmol of 5-methylcytosine. However, the derivatization of modified bases has become less popular because of the possibility of removing this modification by a facile S_N2 reaction.⁵

Three families of modified bases have been the focus of some studies: 5-fluoropyrimidines,¹¹ 2- and 4-thiouracils,^{12,13} 2- and 4-monoseleno- or 2,4-diselenopyrimidines or -purines¹⁴ (Fig. 5). The 5-fluoropyrimidines, initially developed during the search for new antitumor agents, show a marked increase in retro-Diels-Alder fragmentation compared to the nonhalogenated bases.⁹ The position of the sulfur atom in bases can be easily deduced from the EI mass spectra of various thiouracils¹¹ or alkoxyacetylthiouracils.^{12,15} Seleno derivatives are often used in toxicological studies, and their incorporation in the base can be detected, using EI conditions. However, Se or SeH moieties are easily expelled from the molecule during the fragmentation process. Consequently, the molecular-ion intensities of selenouracils are intermediate between those corresponding to their oxygen and sulfur analogs, although the general fragmentation pattern remains essentially similar to that of the parent base. In this respect, the use of mass

⁷ A. E. Pierce, "Silylation of Organic Compounds," Chapters 9 and 10. Pierce Chem. Co., Rockford, Illinois, 1979; *Aldrichim. Acta* **15** (3), 70 (1982).

⁸ M. A. Quilliam and J. B. Westmore, *Anal. Chem.* **50**, 59 (1978).

⁹ J. B. Westmore, M. A. Quilliam, and K. K. Ogilvie, *Adv. Mass Spectrom.* **8**, 106 (1980); *Org. Mass Spectrom.* **16**, 129 (1981).

¹⁰ J. Singer, W. C. Schnute, Jr., J. E. Shively, C. W. Todd, and A. D. Riggs, *Anal. Biochem.* **94**, 297 (1979).

¹¹ T. Marunaka, *Biomed. Mass Spectrom.* **8**, 105 (1981).

¹² E. Wyrzykiewicz, K. Golankiewicz, and M. Stobieck, *Adv. Mass Spectrom.* **8**, 619 (1980); *Org. Mass Spectrom.* **16**, 153 (1981).

¹³ E. Wyrzykiewicz, J. Buczek, and K. Golankiewicz, *Org. Mass Spectrom.* **16**, 221 (1981).

¹⁴ J. G. Liehr, C. L. Weise, P. F. Crain, G. H. Milne, D. S. Wise, L. B. Townsend, and J. A. McCloskey, *J. Heterocycl. Chem.* **16**, 1263 (1979).

¹⁵ E. Wyrzykiewicz and J. Buczek, *Org. Mass Spectrom.* **17**, 403 (1982).

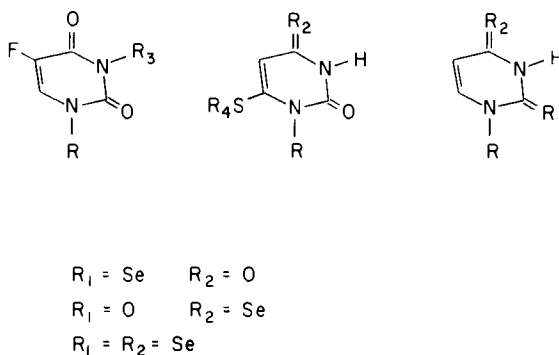


FIG. 5.

spectrometry in toxicological studies on the seleno derivatives of bases, more particularly those reacting with other nucleic acid bases, and on their metabolism is extremely valuable.¹³

Secondary-ion mass spectrometry (SIMS) of a thin layer of nucleic acid bases deposited on a silver foil under bombardment with Ar^+ ions at 3 kV gives intense pseudomolecular ions $[\text{M} \pm \text{H}]^\pm$ but practically no simple bond cleavage fragments.¹⁶ Another new technique is that of (pulsed) laser induced desorption (LD). When applied to nucleotide bases such as cytosine or adenine (266 nm, quadruplet neodymium laser; or 347 nm, ruby laser) the technique has good detection limits, particularly for ions with a short lifetime (up to 100 nsec).¹⁷ The technique makes use of a time-of-flight instrument and is utilized in both modes, positive (PI) and negative ions (NI). Both bases exhibit an intense $[\text{BH}]^+$ ion. These results are similar to those obtained by ^{252}Cf plasma desorption (PD).

III. Nucleosides

The mass spectral behavior of the nucleoside subunits of nucleic acids has been well studied.³⁻⁵ As expected, most of the cleavages take place at the sugar moiety of the nucleoside since bases (purines or pyrimidines) are more stable than sugars and are better at delocalizing charges. The initial ionization, under standard EI conditions, takes place on a base unit of the nucleoside. Consequently, the base and its fragments account for the majority of the important ions. The main fragmentation of nucleosides can be summarized according to McCloskey³ (Fig. 6).

¹⁶ A. Eicke, W. Suchtermann, and A. Benninghoven, *Org. Mass Spectrom.* **15**, 289 (1980).

¹⁷ B. Schueler and F. P. Krueger, *Org. Mass Spectrom.* **15**, 295 (1980).

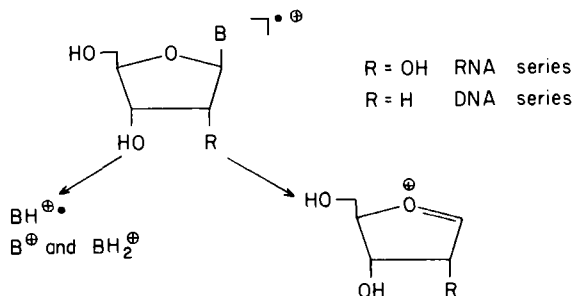


FIG. 6.

The most important ion is usually $[BH]^{\bullet+}$, which of course is very useful for the identification of the base. The origin of the hydrogen on a $[BH]^{\bullet+}$ ion has been established to be the 5'-hydroxy group (Fig. 7), although the 2'-hy-

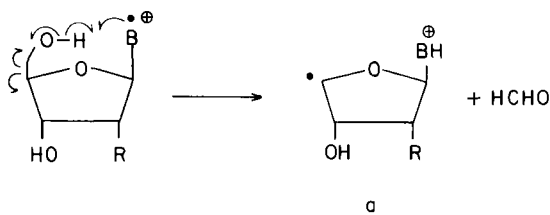
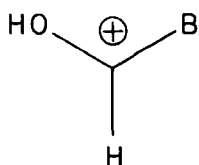


FIG. 7.

droxy or even the 3'-hydroxy group might also be involved in these H-transfer processes to the base. In both of these cases the sugar moiety of the nucleoside undergoes a well documented β -cleavage (Fig. 8). The 3'-H transfer would then be favored even for the lyxo- or xylopentosides, since both have their free 3'-hydroxy group in the β configuration. However, a 5'-H transfer and the simultaneous formaldehyde formation are believed to be the primary origins of $[BH]^{\bullet+}$ ions. Another important cleavage in nucleosides involves the formation of $[BH]^{\bullet+}$ ions resulting from the opening of the sugar ring with the simultaneous loss of CO (Fig. 9). In the latter scheme the H transfer (toward the base) could have any of the above mentioned origins. The isomeric structure of these ions, as advanced by Biemann and McClos-



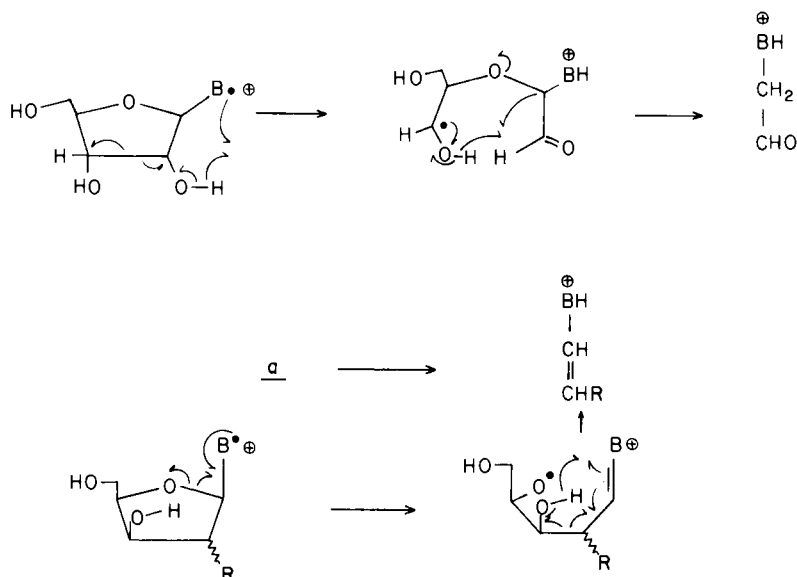


FIG. 8.

key,¹⁸ are based on a deuterium-exchange study at the 2'-hydroxy group, aimed at proving that the origin of the oxygen is 2'. This has not been confirmed for any other essential base in nucleosides. Finally, the fragment $[B + C_4H_4]^+$, less abundant for nucleosides than for the corresponding nucleotides, is obtained by a series of dehydrations and oxidations resulting mainly from the pyrolytic conditions.

The molecular ion is usually present, although very weak, for both guanosine series, as well as $[M - OH]^+$, $[M - H_2O]^+$ and $[M - CH_2O]^+$. Dehy-

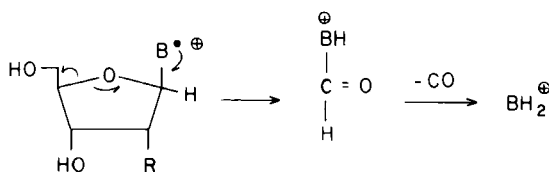


FIG. 9.

¹⁸ K. Biemann and J. A. McCloskey, *J. Am. Chem. Soc.* **84**, 2005 (1962), from D. C. Dejongh, in "Carbohydrate Chemistry and Biochemistry," 2nd ed., Chapter 27, p. 1343. Wiley, New York, 1980.

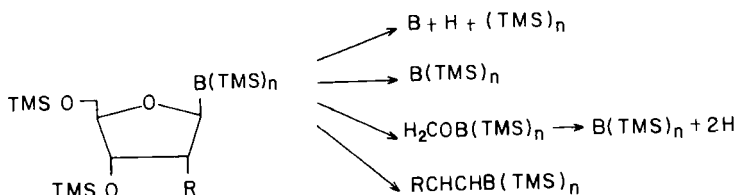


FIG. 10.

dration fragments are more intense for the RNA nucleoside series than for its DNA counterpart.

The quest for better volatility of nucleosides for GC-MS analysis is normally achieved by derivatization. The trimethylsilyls remain the most popular derivatives used in these studies. The silylation of the sugar moiety does not present any interpretation problems. In contrast, the silylation of tautomeric hydroxy or amino groups of the base unit of nucleosides can lead to some misinterpretation. In general, all principal bases, except guanine, undergo monosilylation (disilylation for guanine) as the result of a base-catalyzed silylation reaction (e.g., in pyridine). This derivatization shifts the keto-enol equilibrium toward the enolic form, which is more stable than the corresponding lactam form. The groups $N=C-O-H$ or $N=C-NH_2$ produced under such conditions show an important steric dependence on their geometrical position. Hydroxy or amine moieties located at C-4 are silylated much more easily than any other isomer available via tautomeric equilibration of the base.

The major ions present in the spectra of pertrimethylsilylated nucleosides are similar to those observed for the silylated sugars, i.e., demethylation, disilyl ether formation, loss of TMSOH, TMS^+ , etc.¹⁹ The remaining fragments correspond to the pathways shown in Fig. 10. The molecular ion usually present in the 500–600 amu range is weak and of little value for structure identification purposes. This led to the search for a more stereoselective silylation agent. That goal has been achieved via TBDMSC. It protects the 5'-hydroxyl of common nucleosides except for 2'-deoxyguanosine, which is silylated in the 3' position, because of the slow rotation of the purine on the β side of the nucleoside. The mass spectra of the TBDM-silylated nucleosides show the loss of H_2O from the molecular ion.⁹ Although this silylation has important synthetic chemical applications and the molecular weights of such derivatives are smaller than that of the corresponding perTMS derivatives, it is of little value in GC analysis because of the reduced volatility of these derivatives with respect to their perTMS counterparts.

¹⁹ E.g., K. Jankowski and D. Gaudin, *Biomed. Mass Spectrom.* **5**, 371 (1978).

Other derivatives commonly used in synthesis (trifluoroacetyl, methyl, acetyl, etc.) are of minimal importance in MS analysis of nucleic acids. All derivatives present a common disadvantage in that they are chemical modifications of the original materials and as such have characteristics of their own. This can lead to misinterpretation when confronted with (derivative) sample-related artifacts.

One interesting feature in the mass spectra of trifluoroacetyl derivatives of both ribo- and deoxyribonucleosides is the occurrence of the 2-methylfuran ion²⁰ (Fig. 11), a fragment also found in the pyrolytic mass spectra of nucleotides and nucleic acids. In fact, McCloskey was the first to propose this structure along with that of 4-*exo*-methylenefuran, a rearrangement product of 2-methylfuran.

Guanosine, a low-volatility nucleoside, can be successfully detected by using liquid-ion-evaporation MS-MS.²¹ The positive ion spectrum of this nucleoside in HCl, as obtained from the ion evaporation technique, leads to very intense $[MH]^+$ and $[BH]^+$ ions. However, the analytical utility of this technique, as well as its detection limits, are still uncertain.

The PD and LD spectra of adenine and cytosine nucleosides have been recorded by a German group¹⁷ both in the negative and positive ion modes. Since the former technique shows only a $[BH]^+$ ion in the positive mode, several lower-mass fragments become important for interpretation in the negative ion spectra, particularly the elimination of NH_4 . An intense $[B - H]^-$ ion is also present in both the PD and the LD negative-ion spectra.

The fragmentation of base-modified nucleosides related to cytokinin²² and sugar-modified nucleosides, mainly cyclo- and 2'- and 3'-chloro derivatives,^{23,24} has been reported. However, all of the EI-induced reactions discussed in these reports^{23,24} have already been presented above. Although they do not introduce any new fragmentation pathways, both reports present a

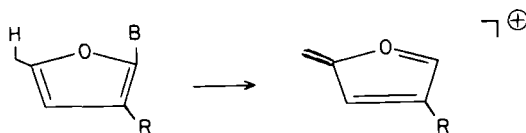


FIG. 11.

²⁰ W. A. Koenig, L. C. Smith, P. F. Crain, and J. A. McCloskey, *Biochemistry* **10**, 3968 (1971).

²¹ B. A. Thomson, J. V. Irzbane, and P. J. Dziedzic, *Anal. Chem.* **54**, 2219 (1982).

²² T. Hashizume, J. A. McCloskey, and J. G. Liehr, *Biomed. Mass Spectrom.* **3**, 177 (1976).

²³ I. A. Mikhailopulo, E. N. Dalinichenko, G. V. Zaitseva, and A. A. Akhrem, *Biomed. Mass Spectrom.* **9**, 225 (1982).

²⁴ P. F. Crain, H. Yamamoto, J. A. McCloskey, Z. Yamaizumi, S. Nishimura, K. Limburg, M. Raba, and H. J. Gross, *Adv. Mass Spectrom.* **8**, 1135 (1980).

detailed discussion of the mechanisms involved and report unambiguous proofs.

Both GC- and LC-MS have been performed on several nucleosides, especially after persilylation, but several problems related to the trimethylsilylation of the N-4 position of cytosine²⁵ as well as 2'-fluoronucleosides²⁶ have been reported. An interesting study of nucleosides using LC-CIMS (ammonia) has been presented.²⁷ That study, along with those of Vestal²⁸ and Melera²⁹ concluded that good spectra of nucleosides can be obtained from "in-line" sample introduction. The best spectra were obtained by spotting a solution of a nucleoside directly onto the LC interface.

The field desorption (FD) literature of nucleosides is not particularly rich. Nevertheless, most of the common nucleosides are reported to give an abundant $[M + H]^+$ ion^{30,31} and, as observed by Wood,³¹ adenosine is used as a reliable standard for FD experiments by various instrument manufacturers.

Finally, the desorption chemical ionization (DCI) mass spectra of several synthetic nucleosides, mostly in the pyrimidine series, have been recorded. The potential application of protonated or cationized (NH_4^+) molecular ions and bases for the detection of these nucleosides has been demonstrated.³² One of the important features of these spectra is the presence of $[B + H]^+$ and/or $[B + NH_4]^+$ ions, which confirms the previously described general fragmentation scheme. In desorption chemical ionization studies (which describe "in-beam" experiments in a CI source), the desorption of intact molecules, followed by ionization, is often confused with the desorption of preformed ions. Slow hydrolysis within a CI source leads to intense ions (e.g., $[BH]^+$) such as those observed for nucleosides,³² as well as for intact DNA.³³

McCloskey³⁴ has studied several cyclonucleosides. The spectra of these compounds containing 2,2', 2,3', 2',6 and 5',6 bonds, have been compared to their corresponding persilylated derivatives. One peculiarity of the uridine

²⁵ K. H. Schram, Y. Taniguchi, and J. A. McCloskey, *Chromatography* **10**, 355 (1978).

²⁶ M. Blandin and K. Jankowski, *Bull. Acad. Pol. Sci.* **27**, 563 (1979); *Eur. J. Mass Spectrom. Biochem. Med. Environ. Res.* **1**, 129 (1981).

²⁷ D. E. Games and E. Lewis, *Biomed. Mass Spectrom.* **7**, 453 (1980).

²⁸ C. R. Blakely, J. McAdamns, and M. L. Vestal, *J. Chromatogr.* **158**, 261 (1978).

²⁹ J. W. Serum and A. Melera, *Proc. 26th Annu. Conf. Mass Spectrom. Allied Top.*, 1978, p. 655.

³⁰ H.-R. Schulten, *Int. J. Mass Spectrom. Ion Phys.* **32**, 97 (1979).

³¹ G. W. Wood, *Tetrahedron* **38**, 1125 (1982).

³² E. L. Esmans, E. J. Freyne, J. H. Vanbroeckhoven, and F. C. Alderweirdt, *Biomed. Mass Spectrom.* **7**, 377 (1980).

³³ K. Jankowski, H. Virelizier, and R. Hagemann, *Biomed. Mass Spectrom.* **10**, 559-566 (1983).

³⁴ S. Tsuboyama and J. A. McCloskey, *J. Org. Chem.* **37**, 2 (1972).

series is the presence of $[\text{BH}]^+$ ion at m/z 112, similar to a normal riboside; similar results have been noted by our group²⁶ for deoxycycloribosides.

Finally, some uridopurines originating from tRNA have been studied by Hecht³⁵ and Posthumus.³⁶

IV. Nucleotides

Nucleotides are monoesters of phosphoric acid (Fig. 12); they show decreased volatility compared to nucleosides, and, consequently, they are less suitable for EI and CI mass spectral studies. Usually, heating of the phosphate moiety leads to the rupture of the phosphate bond and the *in situ* production of the parent nucleoside. It follows that the mass spectra of nucleotides contain, under pyrolytic (Py-EI) conditions, all the characteristics of nucleoside fragmentation once the pyrolysis has cleaved the phosphoester bond.

Early reviews on the mass spectra of nucleotides, more particularly of mononucleotides,^{3-5,37,38} covered trimethylsilyl and methyl derivatives of nucleotides. The silylation of nucleotides, for instance, takes place on the base, on the sugar hydroxyls, and on the free phosphate hydroxyls under mild (room temperature) and basic (pyridine) silylation conditions (BSTFA/TMCS). The fragmentation of derivatives obtained from both procedures has been well studied.^{37,38} Several typical fragments ($[\text{M} - \text{CH}_3]^+$, $[\text{base} + 2\text{H}]^+$, silylated and desilylated sugar, S-TMSOH, etc.), as well as a weak M^+ ion have been recorded. The FD spectrum of an underivatized

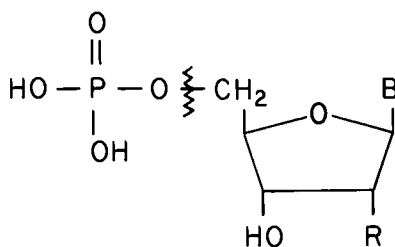


FIG. 12.

³⁵ S. M. Hecht and J. J. McDonald, *Anal. Biochem.* **47**, 157 (1972).

³⁶ M. A. Posthumus, P. G. Kistemaker, H. L. C. Meuzelaar, and M. C. TenNoever de Brauw, *Anal. Chem.* **50**, 985 (1978).

³⁷ A. M. Lawson, R. N. Stilwell, M. M. Tacker, K. Tsuboyama, and J. A. McCloskey, *J. Am. Chem. Soc.* **93**, 1014 (1971).

³⁸ H. Budzikiewicz, *Adv. Mass Spectrom* **6**, 163 (1974).

nucleotide,³⁹ as well as its CI-methane spectrum,⁴⁰ show an important increase in the intensity of the pseudomolecular ion. Plasma desorption (²⁵²Cf) has also been used successfully to record spectra of underivatized nucleotides.^{41,42}

The determination of several modified bases has been achieved by McCloskey, using partial silylation techniques.²⁵ The FD collision-induced-dissociation (CID) mass spectra of a modified nucleotide has been reported by Straub⁴³ during the course of his study on the interaction of a chemical carcinogen with DNA. In that particular experiment, however, the adduct was previously separated by extraction; it was not a direct application of the FD-CID technique to a structural problem. Nevertheless, the study indicated that the attachment of the carcinogenic compound takes place at the base, confirming the potential of this technique for cancer research.⁴⁴

Some novel synthetic nucleoside phosphates have been characterized by EI-MS—particularly 3',5'-phosphoranilidothioates, dioxaphosphorinanes,⁴⁵ and phosphoramidates⁴⁶; their fragmentation behavior is quite usual and predictable.

A study on the quantitative analysis of blood nucleotides by LC-MS or GC-MS of their methylated derivatives has been reported; again derivatization, preconcentration, and summary separation on an XAD column preceded the final identification by GC-MS.⁴⁷

Budzikiewicz⁴⁸ addressed the problems encountered by chemists working on FD-MS of nucleotides. The assignment of ions originating from, e.g., adenosine 3'-monophosphoric acid (or its 5'-isomer) (Fig. 13) has been confirmed. Numerous problems related to desorption temperature, heating rate, and anode deterioration are inherent to the technique.

Field desorption spectra clearly show the cleavage of the phosphate-sugar and the base-sugar bonds. This technique, along with the silylation of the

³⁹ H.-R. Schulten and H. D. Beckey, *Org. Mass Spectrom.* **7**, 861 (1973).

⁴⁰ D. F. Hunt, J. Shabanowitz, F. K. Botz, and D. A. Parent, *Anal. Chem.* **49**, 1160 (1970).

⁴¹ C. J. McNeal and R. D. Macfarlane, *Proc. 25th Annu. Conf. Mass Spectrom. Allied Top.* **1977**, p. 473.

⁴² R. D. Macfarlane, in "Biochemical Applications of Mass Spectrometry" (G. R. Waller and O. C. Dermer, eds.), 1st Suppl. Vol., Chapter 16, pp. 527-566. Wiley (Interscience), New York, 1980.

⁴³ K. M. Straub and A. L. Burlingame, *Adv. Mass Spectrom.* **8**, 1127 (1980).

⁴⁴ A. B. Foster, *Eur. J. Mass Spectrom. Biochem. Med. Environ. Res.* **1**, 3 (1980).

⁴⁵ Z. J. Lesnikowski, W. J. Stec, and B. Zielinska, *Org. Mass Spectrom.* **15**, 454 (1980).

⁴⁶ R. G. Smith and D. Farguhar, *J. Heterocycl. Chem.* **17**, 1659 (1980).

⁴⁷ I. Jardine and M. M. Weidner, *J. Chromatogr.* **182**, 395 (1980).

⁴⁸ H. Budzikiewicz, *Biomed. Mass Spectrom.* **4**, 103 (1977); H.-R. Schulten and H. D. Beckey, *Org. Mass Spectrom.* **7**, 861 (1973); H.-R. Schulten and H. M. Schiebel, *Fresenius' Z. Anal. Chem.* **280**, 139 (1976).

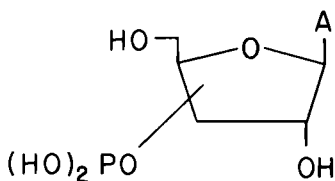


FIG. 13.

nucleoside 2'-3'- or 5'-monophosphate isomers, leads to an unambiguous determination of the phosphate position on the nucleoside skeleton and to its structure determination. It should be noted, however, that the distinction between these phosphates is achieved more easily by using high performance liquid chromatography (HPLC).⁴⁹

Desorption chemical ionization spectra of several nucleotides have been discussed by Esmans.³² Similar to nucleosides, protonated or positively charged molecular and base ion intensities are dramatically improved with respect to the silylated analogs of free nucleotides.

A liquid ion evaporation MS-MS study has been reported for nucleotides that usually do not produce intense molecular ions.²¹ It was suggested that this technique might be superior to ²⁵²Cf PD, CI-MS, DCI, FAB, secondary ion mass spectrometry (SIMS), and ion thermospray for some compounds of great biochemical importance such as adenosine triphosphate (ATP).

A biochemically important pair of compounds, namely, NAD-NADH, together with a series of model nucleotides, have been investigated by LD and PD.⁵⁰ Two laser beams were used in that experiment (266 and 347 nm), and the results were compared to those obtained by ²⁵²Cf PD. For simple nucleotides the major ions produced during LD processes are not dependent on the wavelength used. However, the results obtained for NAD-NADH (positive and negative mode) do not follow that trend. Although the exact reason for these differences is still unknown, it can be speculated that an interaction between wavelength and the resonance forms of the aromatic base can account, in part, for this deviation in pattern.

Finally, SIMS of nucleotides¹⁶ show intense quasimolecular ions in the 100-400 amu region. The newest technique, fast atom bombardment (FAB) has been applied to the characterization of N-7 alkylated quanosine monophosphates.⁵¹ Fenselau and her group dealt successfully with these

⁴⁹ J. J. Kirkland, *Chromatogr. Sci.* **8**, 72 (1970).

⁵⁰ B. Schueler, see Ref. 17, and references quoted therein.

⁵¹ C. Fenselau, V. T. Vu, R. J. Cotter, G. Hansen, D. Heller, T. Chen, and O. M. Colvin, *Spectrosc. Int. J.* **1**, 145 (1982).

zwitterions, using both PI and NI mass spectra. Mass spectra of quaternary bases always presented a challenge to mass spectrometrists (particularly in the amino-acid field). Fenselau reported on the identification of N-alkylated quaternary salts under FAB conditions, more particularly on the side chains. No obvious differences in the overall sensitivity between NI and PI were found. That study is an excellent starting point for a better understanding of the relative stability of covalent bonding in common FAB matrices.

A last problem in nucleotide mass spectrometry is related to the dinucleotides. Hunt⁵² and Hignite⁵³ tried to prepare a matrix of several ribodinucleotides (silylated) for further application to the sequential analysis of oligonucleotides. The fact that common enzymatic and/or chemically induced hydrolyses do not stop at the nucleotide level, but rather continue until they become nucleosides, does not reduce the merit of their work. That work, as well as that of Biemann,⁵⁴ enable one to identify any dinucleotide pair of the type B₁pB₂, where p stands for phosphate. This information is of very limited use, however, because from any given RNA, for instance, one obtains practically any possible B₁pB₂ combination of dinucleotides.

This approach to persilylated dinucleotide structure study is based on the predominant cleavage of the phosphate bond from the 5' ester side rather than the 3'. This peculiar difference in ion intensities is used advantageously in FAB studies of polynucleotides (see below). It is very difficult to deal with persilylated fragments of molecular weights around 1000 amu. A parallel degradation on silylated dinucleotides, using phenylboronates or acetanides as an additional marker was performed by Wiebers.⁵⁵ It gave more accurate sequential information about the structure. Nevertheless, the previous comment about the molecular weight limitation still remains. In other words, sequential analysis of polynucleotides cannot be achieved by silylation or partial degradation methods. The future of polynucleotide sequence analysis appears to be closely related to the use of FAB or to some modification of existing time-of-flight (TOF) techniques where high mass analysis is a less severe limitation.

Fragments of B₁pB₂ originating from underivatized DNA have also been observed under FD⁵⁶ and DCI⁵⁷ conditions; again, their analytical use is very

⁵² D. F. Hunt, C. E. Hignite, and K. Biemann, *Biochem. Biophys. Res. Commun.* **33**, 378 (1968).

⁵³ C. E. Hignite, Ph. D. Thesis, MIT, Cambridge (1969).

⁵⁴ K. Biemann and C. E. Hignite, *Org. Mass Spectrom.* **2**, 1215 (1969).

⁵⁵ J. L. Wiebers and J. J. Dolhun, *J. Am. Chem. Soc.* **91**, 7755 (1969).

⁵⁶ H.-R. Schulten, H. D. Beckey, A. J. Boerboom, and H. L. C. Meuzelaar, *Anal. Chem.* **45**, 2358 (1973).

⁵⁷ K. Jankowski, J. R. J. Paré, H. Virelizier, and D. Gaudin, in "Mass Spectrometry in Biomedical Sciences" (A. Frigerio, ed.), Chapter 7. Elsevier, Bordighera, Italy, 1982.

limited. From a mechanistic standpoint, it is highly improbable that DNA phosphate would cleave through some orderly scheme of poly-, tri-, di-, and mononucleotide fragments rather than through a random cleavage of phosphate bonds. The only direct use of the B_1pB_2 fragments is related to the knowledge of the immediate neighborhood of modified base nucleotides.

V. Nucleic Acids and Polynucleotides

These two classes of compounds can be classified as diesters of phosphoric acid. Their mass spectrometric behavior must follow the fragmentation guidelines established for simpler esters with the differences that: (1) pyrolysis will cleave the phosphate bond with extrusion of a 2-methylfuran unit and its polymers and (2) we are dealing with natural polymers of extremely low volatility and extremely high molecular weight.

The 3'- and 5'-phosphodiester, as presented in Fig. 14, show an important difference in the stability of their 3'- and 5'-phosphate bonds. The former can be seen as a secondary alcohol ester, the latter (5') as a primary. The cleavages of both phosphates occur easily although the 5'-cleavage (leading in turn to more intense ions) predominates.^{57,58} All possible cleavages take place: $3'O-P$, $5'O-P$, $3'C-O$ and $5'C-O$, thus leading to numerous nucleoside ions. The phosphate cleavages from both ends of the nucleic acid take place simultaneously. Nucleoside ions and sometimes dinucleotide ions are observed under EI conditions. However, tri- and higher nucleotide fragments are absent from the spectra.

It is difficult to establish who recorded the very first spectrum of native nucleic acid material; certainly many spectrometrists were working with

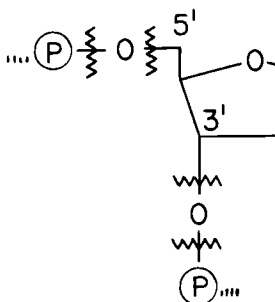


FIG. 14.

⁵⁸ K. Jankowski and D. Gaudin, *Org. Mass Spectrom.* **15**, 78 (1980).

nucleoprotein material. It appears that the first spectrum of underivatized DNA, recorded under pyrolytic conditions, was reported by Charnock and Loo.⁵⁹ However, pyrolysis of nucleic acids was not recognized as an important analytical procedure until several years later. This is well illustrated by a 1976 report from Levsen⁶⁰ showing that the six major components from the pyrolysis of DNA, recorded under collisional activation conditions, were methanol, acetonitrile, furan (and 2-methylfuran), propargyl alcohol, α -angelica lactone and furfuryl alcohol. No single comment was made about the presence of DNA base ions and the general appearance of a DNA spectrum. McCloskey⁶¹ and Biemann⁶² opted to work with hydrolysates rather than with intact nucleic acids. Wiebers⁶ has reported a first systematic examination of nucleic-acid spectra of different origin.

Figures 15 and 16 show typical Py-EI mass spectra of herring-sperm DNA and yeast RNA recorded on a Riber 1010 quadrupole mass spectrometer. The spectrum of the synthetic polynucleotide polydeoxyinosine-deoxycytosine⁶³ (Fig. 17), recorded in a negative ion mode (e^- capture), shows the essential characteristics of this polymer (m/z 135; B^- for I and 110; B^- for C) as expected.

The pyrolysis of nucleic acids generally occurs between 200 and 250°C, using a normal direct inlet probe. In order to decrease the possible contamination of the mass spectrometer, different pyroprobes^{6,58,59,64} or even flash

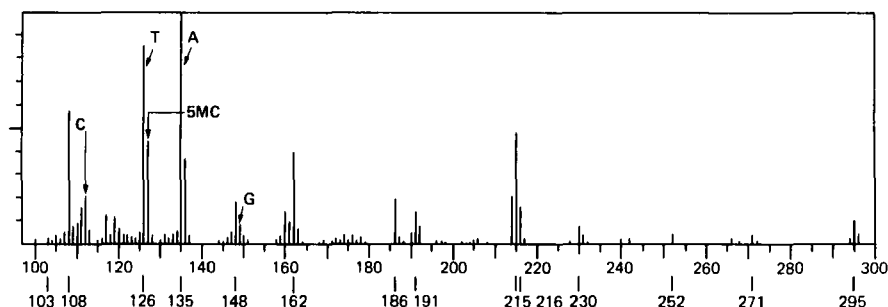


FIG. 15. DNA herring sperm; Riber 1010 EI, PI (70 eV, 250°C).

⁵⁹ G. A. Charnock and J. L. Loo, *Anal. Biochem.* **37**, 81 (1970).

⁶⁰ K. Levsen and H.-R. Schulten, *Biomed. Mass Spectrom.* **3**, 137 (1976).

⁶¹ A. M. Lawson, W. A. Koenig, L. Smith, N. R. Earle, and J. A. McCloskey, *Adv. Mass Spectrom.* **5**, 753 (1971).

⁶² D. F. Hunt, C. E. Hignite, and K. Biemann, *Biochem. Biophys. Res. Commun.* **33**, 368 (1968).

⁶³ Sample of poly d (I,C) was a gift from Dr. W. Guschlbauer (CEN de Saclay, France).

⁶⁴ K. Jankowski, J. P. Macquet, and J. L. Butour, *Biochem. Biophys. Res. Commun.* **92**, 68 (1980); Submitted for publication.

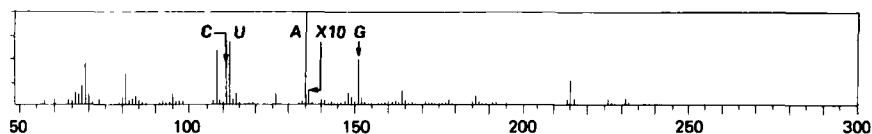
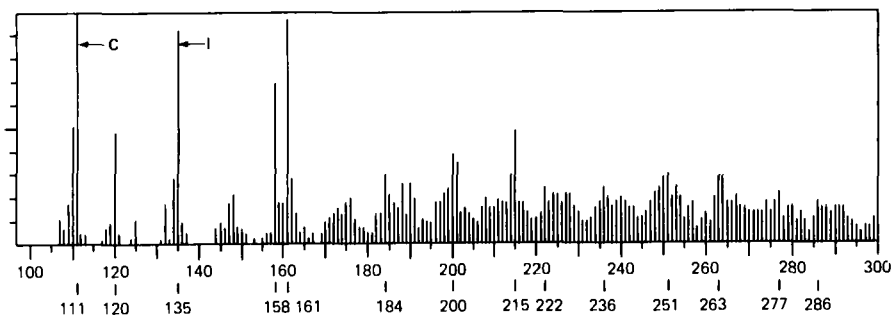


FIG. 16. RNA Mann yeast; Riber 1010 EI, PI (70 eV, 250°C).

pyrolytic units⁶⁵ have been used. The pyrolysis temperature does not appear to have an important influence on the nature of the fragments recorded; however, their relative intensity is slightly affected for EI, whereas in CI, DCI, and FD it exhibits a dramatic temperature dependence.³³

The general fragmentation scheme for intact DNA under Py-EI conditions has been proposed to a large extent by Wiebers⁶; it is summarized in Figure 18. The cleavage of the phosphodiester bond produces a nucleoside fragment and a 2-methylfuran unit (m/z 81), which can combine to give ions **b** or **c** or eventually add to a PO_3 unit to form an **a/b** ion (see Fig. 18).⁵⁸ This dualism in the behavior of DNA has been confirmed by an exact mass measurement study. Two similar structures are possible for the ion **d**: cleavage of the base, allowing attachment of the base fraction to a phosphate and to a fragment of a sugar ring, or to a structure composed of the base and a fragment of a sugar ring. It is interesting to note that the bond linking the phosphodiester to the stable aromatic base does not undergo cleavage until the late formation of the ion **d**.

The nucleoside-like behavior of fragment **a** gives the most intense BH ions (Fig. 18). In such a manner the EI-MS of any normal DNA shows a series of BH ions at m/z 135 (A), 126 (T), 111 (C), and 151 (G) where the latter is of lesser intensity. All of these fragments appear in the 100–200 amu area. The

FIG. 17. Poly d(I, C); Riber 1010 NI, e^- capture.

⁶⁵ K. Jankowski, *Abstr. Chem. Congr. North Am. Continent, 2nd, 1980, Paper Anyl 54 (1980)*.

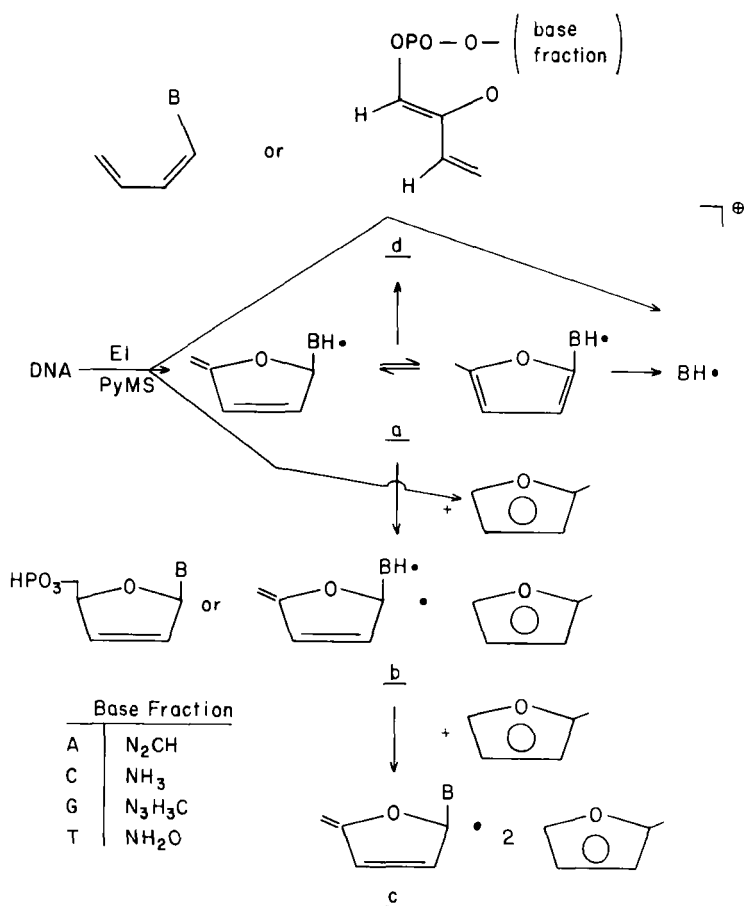


FIG. 18.

rest of the EI spectrum shows ions **a**, **b**, and **d**, but very few, if any, other intense ions. However, in an FD spectrum the presence of dinucleotides (usually doubly charged) is observed. This is the smallest polynucleotide unit observed⁶⁶⁻⁶⁹; again their usefulness to the DNA problem is very limited.

These first applications of mass spectrometry to nucleic acid or polynucleotide analysis are, in effect, a qualitative verification of the presence of base units. However, these studies initiated a quantitation of the base abundances, using the intensities of BH fragments. The method gives data very

⁶⁶ H.-R. Schulten and H. M. Schiebel, *Fresenius' Z. Anal. Chem.* **280**, 139 (1976).

⁶⁷ H.-R. Schulten and H. M. Schiebel, *Nucleic Acids Res.* **3**, 2027 (1976).

⁶⁸ D. E. Games, *Biochem. Soc. Trans.* **3**, 455 (1977).

⁶⁹ H. J. Veith, *Tetrahedron* **33**, 2825 (1977).

similar to those obtained in the GC analysis of the reaction mixture obtained from the acidic digestion and the derivatization of polynucleotides. The mass spectrometric method is, of course, less laborious and less expensive than the enzymatic digestion usually performed by biochemists. In particular, the use of *endo*- and *exo*-nucleases can be completely eliminated.⁷⁰

In a qualitative study on pyrolytic spectra of nucleic acids, McCloskey⁷¹ established the structures of several modified nucleosides in tRNA. These hypermodified nucleosides play an important role in the understanding of the action of tRNA. At this time all structures of hypermodified bases, as suggested from simple BH^+ ions, have been supported by other physico-chemical data including NMR, FTIR, and laser Raman. Manipulation of intensity data for two or more ions within the same family (e.g., BH) can help identifying the so-called modified bases. One of the earliest examples was the identification of 5-chlorocytosine, along with cytosine, in DNA hydrolysate. The deviation from 1 : 1 ratios for A : T or C : G is a first indication of the presence of modified bases and, in this case, the total cytosines must include 5-chlorocytosine in order to yield the correct ratio. Therefore, the ratio of any pair of matching bases $B_1 : B_2$ is related to the abundance ratio of similar bases in DNA. By analogy, a deviation from the 1 : 1 ratio of bases involved in normal Watson-Crick pairing is a strong indication of the presence of modified bases.

Naturally, the next application was aimed at the quantitation of this relationship. The ratio of 5-methylcytosine : cytosine in DNA was determined by mass spectrometry, using multiple selected ions monitoring, for ϕ -174 DNA as well as for DNA originating from calf thymus, salmon sperm, and several other sources.⁷² It must be noted however, that these GC-MS data were obtained from hydrolysates of the whole DNA.

Base quantitation on eight microbial DNAs has been achieved by Wiebers⁷³ using an interesting approach. The intensities of all common base BH ions have been summed and expressed as an individual deflection D_x :

$$D_x = \frac{I_{B_1}}{\sum I_{B_n}}$$

⁷⁰ H. A. Sober, ed., "Handbook of Biochemistry: Selected Data for Molecular Biology," p. H20. Chem. Rubber & Publ. Co., Cleveland, Ohio, 1968.

⁷¹ J. A. McCloskey and S. Hishimura, *Acc. Chem. Res.* **10**, 403 (1977).

⁷² A. W. Lis, R. K. McLaughlin, D. I. McLaughlin, G. D. Daves, Jr., and W. R. Anderson, Jr., *J. Am. Chem. Soc.* **95**, 5790 (1973).

⁷³ J. L. Wiebers and D. M. Hawley, *Nucleic Acids Res.* **5**, 4949 (1978); J. L. Wiebers, *Anal. Biochem.* **51**, 542 (1973); J. L. Wiebers and J. A. Shapiro, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **34**, 607 (1975); J. L. Wiebers and J. J. Dolhun, *J. Am. Chem. Soc.* **91**, 7755 (1969); J. L. Wiebers, *Adv. Mass Spectrom.* **5**, 757 (1970; also see *Abstr. Chem. Congr. North Am. Continent, 1st*, 1975, Abstract 62 (1975)).

Each deflection has been plotted against a known composition (abundance) of bases, and standard curves have been prepared for the four common DNA bases. The sensitivity of the method has been established to subnanogram levels, assuming that all spectra are recorded under identical conditions (pyrolysis time, temperature, etc.) and on relatively pure DNA. Although the BH ions are unique and there is no interference from the nucleoprotein peaks, the Wiebers curves work well only for bacteriophage DNA; they fail when tested on DNA obtained from other sources.

Our group⁷⁴ proposed calibration curves for the four bases, again under rigorously similar pyrolytic conditions. The curves were obtained from a spectral compilation of over 60 different DNAs (Fig. 19). Although in general the application of our curves gives better results, it remains that such a statistical study is of very limited use. The four equations for the calculation of base abundances from the ion intensities are $A = 0.61 D_A - 0.35$, $C = 1.07 D_C + 2.1$, $G = 1.46 D_G + 12.1$, $T = 0.74 D_T + 6.8$, where D_x is the deflection of any given base.

These four equations represent better standard curves than those presented by Wiebers in terms of relative agreement and of correlation factors.

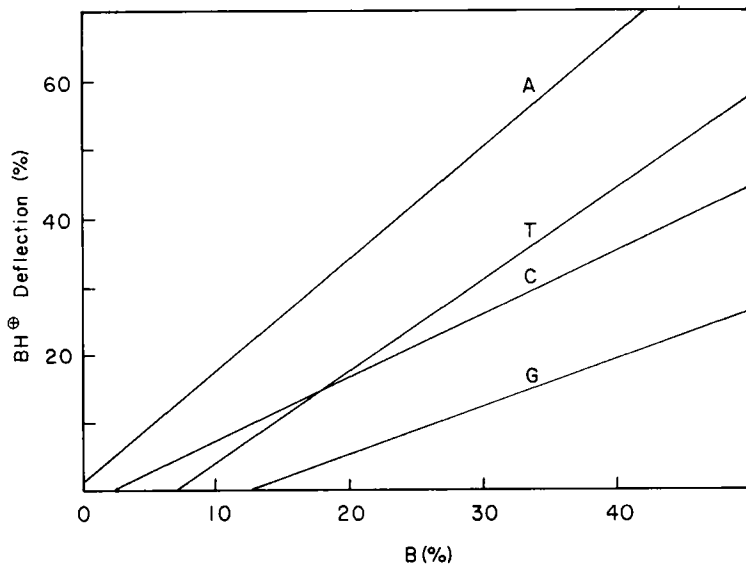


FIG. 19. Plot for quantitative evaluation of B in DNA.

⁷⁴ K. Jankowski, N. Turkkan, and F. Söler, *Biomed. Mass Spectrom.* **9**, 91 (1982).

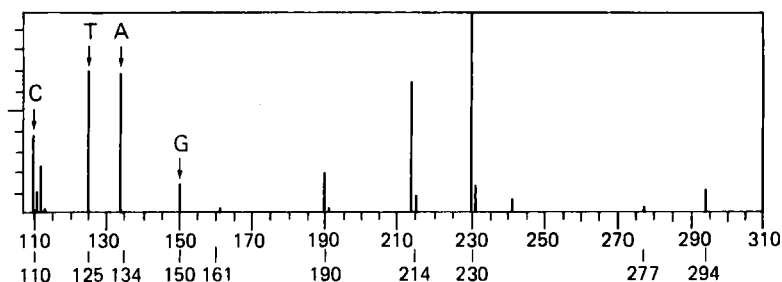


FIG. 20. DNA herring sperm; Riber 1010 DCI, NI, e^- capture.

Continuing our search for a semiempirical relationship between deflection and abundance for any given base we have introduced⁷⁵ the approach of monitoring three ions per base (ions **b**, **d**, and **BH**, Fig. 18). A semiempirical formula, more complicated than the previous one, provides the means to evaluate the abundance of the base directly from the mass spectrum. The parallel search for a better understanding of the fragmentation mechanism and to improve the sensitivity of the methods continues. Wiebers⁶ recorded spectra on one A260 unit of DNA, using Py-EI methods; the actual limits have now been lowered to 10^{-3} A260 unit of DNA, using a CI positive ion, and down to 10^{-5} A260 unit, using CI in the negative mode.⁵⁷ These limits are much better than those achieved by EI.³³ Table III⁷⁶ shows some typical fragments recorded, using EI and CI (DCI) for eight DNA bases; the BH^{+} ion (positive mode) has been replaced by an intense B^- ion in the negative mode. The choice of a good reagent gas has been discussed by our group,³³ and the results of that systematic study are presented in Table IV. Figures 20 and 21 show typical spectra of DNA (herring sperm) recorded under negative DCI conditions (e^- capture) and in positive mode (CH_4), respectively.

The conclusion of our study is that a most sensitive spectrum can be obtained, using NI electron capture or using OH^- (from an N_2O /hydrocarbon mixture) as reagent gas. The sensitivity achieved for the G ions is better by using this method. In the PI mode, isobutane or methane DCI spectra offer the best overall sensitivity (Figs. 22 and 23).

Identification of modified or hypermodified bases has been reported by Py-EI collision-activation mass spectrometry⁷⁷ for tRNA. As mentioned

⁷⁵ K. Jankowski and F. Söler, *Eur. J. Mass Biochem. Med. Environ. Res.* **2**, 33 (1982); **1**, 45 (1980).

⁷⁶ K. Jankowski, in "Mass Spectrometry in Biomedical Sciences" (A. Frigerio, ed.), Chapter 18. Elsevier, Venice, 1981.

⁷⁷ G. Puzo and J. L. Wiebers, *Nucleic Acids Res.* **10**, 328 (1982).

TABLE III
TYPICAL IONS OBSERVED UNDER VARIOUS IONIZATION CONDITIONS^a

Base	EI-PI	EI-NI	DCI	
			PI (NH ₃ /methane)	NI (<i>e</i> ⁻ capture)
DNA				
A	135(BH ⁺)	134(B ⁻)	136	134
G	151	150	152	150
C	111	110	112	110
T	126	125	127	125
5MC	125	124	126	124
HMC	141	140	142	140
HMA	149	148		
I	136	—		
RNA (four major only)				
A	135(BH ⁺)	134(B ⁻)		
G	151	150		
C	111	110		
U	112	111		

^a All spectra were recorded under pyrolytic conditions.^{33,57,76}

before, such RNA is of particular interest because of the numerous modified nucleosides present. The precise determination of the structure of minor (up to 1%) nucleosides is possible and the tRNA can be used without derivatization. Two minor bases, namely, 1-methyladenine and 5-methylcytosine, have been detected in DNA from mass-analyzed ion kinetic energy spectral

TABLE IV
REAGENT GASES USED IN DCI STUDY OF DNA^a

Reagent gas	PI	NI
Electron capture	—	<i>e</i> ⁻
CH ₄	H ⁺	—
<i>i</i> -C ₄ H ₁₀	H ⁺	—
NH ₃	H ⁺ , NH ₄ ⁺	—
Cl ₂	Cl ⁺	Cl ⁻
HCl	H ⁺ , Cl ⁺	—
N ₂ O/CH ₄	—	OH ⁻
CH ₄ /H ₂ O	—	OH ⁻
N ₂ O/ <i>i</i> -C ₄ H ₁₀	—	OH ⁻
CCl ₄ , CHCl ₃	—	Cl ⁻

^a Herring sperm DNA (see Ref. 33).

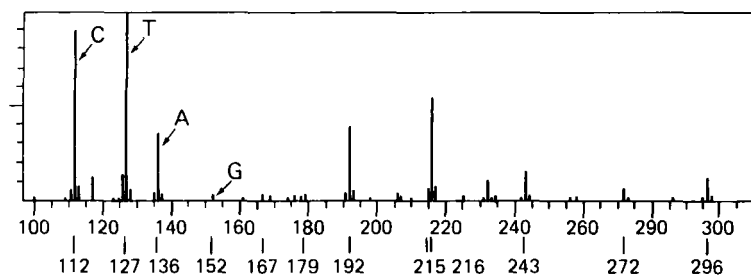


FIG. 21. Herring sperm DNA; Riber 1010 DCI, PI, H^+ (CH_4).

(MIKES) data,⁷⁸ and the origins of several ions have been established by the same group, e.g., for *E. coli* DNA.⁷⁹

Ribonucleic acid has been studied less intensely by mass spectroscopy. A typical mass spectrum, such as that presented in Fig. 16, shows several features. The general fragmentation pattern is similar to that of DNA (Figs. 18 and 24). As observed by Hecht³⁵ and later quantified by McCloskey,⁸⁰ mass spectra of RNA show numerous B^- ions, which may be assigned to two ions for the nucleoside (with and without 2'-OH), the base plus part of the

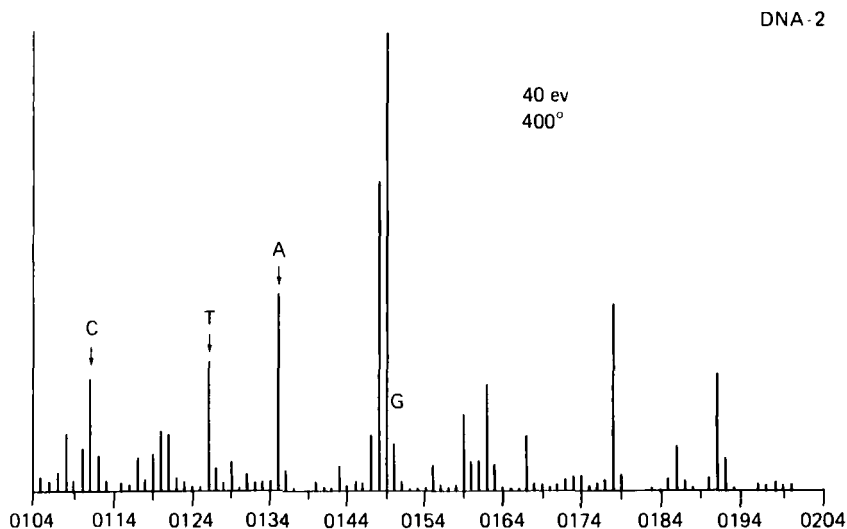


FIG. 22. Salmon sperm DNA; Riber 1010 EI, PI (40 eV, 400°C).

⁷⁸ A. E. Schoen, R. G. Cooks, and J. L. Wiebers, *Science* **203**, 1249 (1979).

⁷⁹ M. H. Bozorgzadeh, J. H. Beynon, and J. L. Wiebers, *Adv. Mass Spectrom.* **8**, 971 (1980).

⁸⁰ P. F. Crain, H. Yamamoto, J. A. McCloskey, Z. Yamaizumi, S. Nishimura, K. Limburg, M. Raba, and H. J. Gross, to be published.

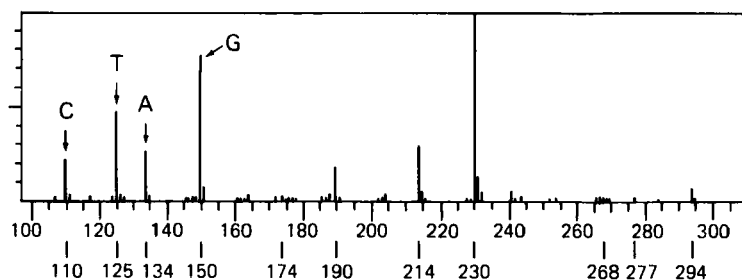


FIG. 23. Herring sperm DNA; Riber 1010 DCI, NI, OH^- ($\text{N}_2\text{O}/\text{CH}_4$).

sugar (with and without 2'-OH), and another fragment at m/z 108. It is probable that this fragment, reported by Weibers in the DNA spectrum to be of adenosine origin,⁶ contains a phosphate moiety. The four essential bases are present in the spectrum (PI, EI, Py), particularly $[\text{BH}]^+$ ions for A (m/z 135), C (m/z 111), and G (weak at m/z 151), and uridine instead of thymine gives a new peak at m/z 112.

Thus both qualitative and quantitative evaluations of bases, and modified bases, make important contributions toward a potential routine diagnostic tool. Let us examine two specific examples, both related to cancer.

Platination of DNA usually takes place on a G-C base pair; it breaks the hydrogen bond between the two bases, thus causing shrinkage of the DNA. This selective action of, for example, *cis*-dichlorodiamminoplatinum

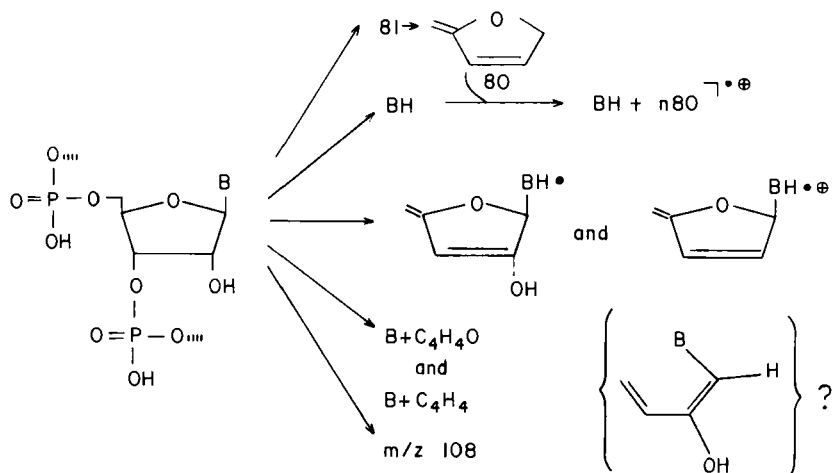


FIG. 24. RNA fragmentation (Py EI).

toward DNA has been studied because of its potential anticancer effects. We have studied different complexes between *cis*-platinum and DNA and have found several modifications in the G–C pair area. The Py–EI spectrum^{64,81} shows the possibility of a hydrogen shift within this base pair when platination takes place. This shift is dependent on the geometry of the complexes and for *trans*-platinum it is of secondary importance. An important question remains unanswered by these data: are they simply another proof for the presence of a hydrogen bond between these two bases or do they provide some evidence on the action of *cis*-platinum as a cancer chemotherapeutic? There is no doubt about the complexation site. The most basic or nucleophilic center (G) involved can be detected by modifying the DNA through some form of titration of the platinated DNA by mass spectrometry in order to localize a maximum of interactions between DNA and *cis*-platinum. Following these studies, Wiebers⁸² investigated the adducts formed between DNA and other platinated models by EI and FAB⁸³ and confirmed the site of complexation to be at N-7 of the guanine residue.

Similar studies have been performed on DNA under carcinogenesis conditions. For instance, Wiebers⁸⁴ studied the adducts between DNA and some aromatic polynucleic compounds, demonstrating that Py–MS can be used in the study of the mechanism of carcinogenesis. We reached similar conclusions⁸⁵ working with ellipticine, another potential antitumor compound.⁸⁶ The characterization of major adducts between either a carcinogenic agent and DNA or between chemotherapeutics and DNA is therefore possible despite some experimental complications brought about by the purification of such adducts. The future of similar applications in the field of cancer studies looks very promising.^{44,87}

The positive-ion FAB spectrum of ATP (sodium salt) and negative ions of NAD have also been recorded.⁸⁸ In both cases intense pseudomolecular

⁸¹ K. Jankowski, J. P. Macquet, and J. L. Butour, *Biochimie* **60**, 1048 (1979).

⁸² N. P. Johnson, J. P. Macquet, J. L. Wiebers, and B. Monsarat, *Nucleic Acids Res.* **10**, 5255 (1982).

⁸³ G. Puzo, J. C. Promé, J. P. Macquet, and I. A. S. Lewis, *Biomed. Mass Spectrom.*, in press.

⁸⁴ J. L. Wiebers, P. J. Abbott, M. M. Coombs, and D. C. Livingston, *Carcinogenesis (London)* **2**, 637 (1981).

⁸⁵ K. Jankowski, Unpublished data (work in progress).

⁸⁶ A. Gouyette, R. Reynaud, J. Sadet, M. Baillavgi, C. Gaussev, S. Cros, F. Le Goffic, J.-B. LeBecqu, C. Paoletti, and C. Viel, *Eur. J. Med. Chem.* **15**, 503 (1980).

⁸⁷ O. Stokke, *Biomed. Mass Spectrom.* **3**, 97 (1976); P. Vigny, M. Spiro, F. Gaboriau, Y. Le Beyec, S. Della Negra, J. Cadet, and L. Voituriez, *Int. J. Mass Spectrom. Ion Phys.* **53**, 69 (1983).

⁸⁸ M. Barber, R. S. Bordoli, R. D. Sedgwick, and A. N. Tyler, *Nature (London)* **293**, 270 (1981); *J. C. S. Chem. Commun.*, 325 (1981).

$[M + 1]^+$ [or $[M - 1]^-$] ions have been observed. Williams⁸⁹ has reported the FAB negative-ion spectrum of a tetranucleotide, reaching the molecular weight of 1172 amu, using a modified Kratos MS-50 and argon bombardment. Sindona⁹⁰ also reported a spectrum of a nucleotide, using the same technique. Neither of these authors dealt with the sequence analysis problem.

VI. Sequence of Ribo- and Deoxyribonucleotides and Nucleic Acids

Early studies in this field were limited to the trinucleotide level. Because of the high molecular weights and the low volatility involved, mass spectra of polynucleotides did not appear to have much of a future. This led Wiebers⁹¹ to draw rather pessimistic conclusions about the future of the technique in terms of direct sequence analysis, without eventually having to resort to extensive derivatization or to partial degradation.

One of the early interesting findings came from the work of Schulten⁹² on two isomeric dinucleotides CpA and ApC, using FD-MS. He observed completely different spectra for these two isomeric compounds in terms of the presence of specific ions and the relative intensities of common ions. Generally, unambiguous identification of the sequence of any nucleotide is not possible, exception made of GpU (weak G-origin peaks) and the above mentioned pair of nucleotides, unless additional information is available.

Work combining MS and degradation data have also been presented.^{91,93} Oxidative elimination of the polynucleotide with periodic acid cleaves the 3'-connected nucleotide chain. The terminal base thus liberated is then analyzed, and the process is repeated until the end of the sequence. Another report combined MS with enzymatic digestion data,⁹¹ in particular, the selective cleavage by venom phosphoesterase of the oligonucleotide chain from the 3' end. The separation of nucleotides on a Dowex column and subsequent derivatization leads to the determination of both 5' and 3' terminal nucleotides according to Scheme 1.

Wiebers's work⁹¹ on $(N_1pN_2)_n$ polynucleotides led to the assessment of 5' and 3' terminal diagnostic ions from derivatized material (presented in Table V). However, the method fails for complex polynucleotides of unknown structure and is more tedious and more expensive than radio-labeling

⁸⁹ D. H. Williams, C. Bradley, G. Bojesen, S. Santikarn, and L. C. E. Taylor, *J. Am. Chem. Soc.* **103**, 5700 (1981).

⁹⁰ G. Sindona, N. Uccella, and K. Weclawek, *J. Chem. Res., Synop.*, 184 (1982).

⁹¹ J. L. Wiebers, *Anal. Biochem.* **51**, 542 (1973).

⁹² H.-R. Schulten and H. M. Schiebel, *Fresenius' Z. Anal. Chem.* **280**, 139 (1976).

⁹³ J. L. Wiebers, *Adv. Mass Spectrom.* **5**, 757 (1970).

sequential analysis, using biochemical degradation and radiochromatograms.⁹⁴

Sequence									
N_1	p	N_2	p	N_{n-2}	p	N_{n-1}	p	N_n
1. phosphodiesterase									
2. Dowex workup									
3. derivatization									
4. MS									
N_1	p	N_2	p	N_{n-1}	pN_n	3' terminus (identification)		
1-4 cycle									
N_1	p	N_2	p	N_{n-2}	pN_{n-1}	3' terminus (identification)		
etc.									
N_1^a	p	N_2			pN_2	3' terminus (identification)			
1-4 cycle									
N_1	p or N_1	N_1	5' terminus (identification)						

SCHEME 1. Wiebers's combined MS-enzymatic sequence analysis method. ^a At the dinucleotide level one can already make an identification of the remaining sequence (FD). N_n stands for nucleoside.

Another series of sequence analysis originating from the same group is based on the ratios of ions preselected in terms of the nucleotide pairs studied (e.g., A : C, T : C) and on their relative loading. This analysis yields a two-dimensional representation (or map) of species containing high and low levels of any particular nucleotide. The factor analysis reported was not a solution to the sequencing problem and became worse with increasing molecular weight, e.g., hexanucleotides. A positive point about the method is the use of eight ions per nucleotide and their intensities. However, the ease of identification is highly dependent on the absolute intensity of the ions; some are too weak to be significant. The sum of carefully chosen intensities leads to a

TABLE V
DIAGNOSTIC TERMINAL IONS

Nucleotide	5'	3'
T	293	278
C	374	359
A	389	383
G	414	399

⁹⁴ C. F. Brunk and L. Simpson, *Anal. Biochem.* **82**, 455 (1977).

better detection of intense ions, e.g., A- and C-origin ions rather than T- and G-, and to a more exact sequential analysis of A- and C-containing polynucleotides.

Using similar calculations, Wiebers developed a series of computer programs to treat dinucleoside monophosphates of N_1pN_2 type⁹⁵ up to tetranucleotides⁹⁶ by a so-called pattern-recognition technique. This method, based on a sophisticated selection of peak heights, intensities, or on linear combinations of various intensity ratios, allows the mapping of some of these features for any given nucleotide pair having its own proper position. Sequential information can be extracted from these positions. Another method of computerized pattern recognition, developed by Kowalski,⁹⁷ was applied to the sequencing of nucleic acids. In its present form it does not guarantee a high level of reliability. A possible application of such an approach lies in an in-line, computer-aided analysis, but because of the weak intensities of particular ionic species, it is of questionable use and not applicable to Py-EI mode on low resolution mass spectrometers. This approach can be seen as an extension of previous work on dinucleotides but, again, does not offer any possible application to high-molecular-weight DNA, where practically all combinations of neighboring dinucleotides are possible.

Another interesting approach was applied to the pyrolytic mass spectrometry of polymers and might eventually be directed toward nucleic-acid sequence analysis. Linked scan techniques,⁹⁸ based on the formation of metastable ions in a field-free region of the mass spectrometer, allow the study of characteristic sequences up to a relatively high mass region. The information, obtained by pyrolytic-electron impact-induced degradations of the polymers at low ionization energy (~ 15 eV), could lead to the establishment of a polynucleotide sequence. In fact, they could be seen as repetitive segments of a larger chemical identity (range of m/z up to 4000 is expected).

Latest results have been obtained by both ^{252}Cf plasma desorption and FAB. The former is an ongoing study by Macfarlane on a decanucleotide (molecular mass ~ 4000); results on the sequence analysis are not yet available.⁹⁹ The sequencing of a fully protected oligonucleotide, using 5'- and 3'-exonucleases has been proposed for one heptanucleotide, using ^{252}Cf -plasma desorption mass spectrometry. For that type of work the negative ion mode was shown to be fast and reliable.¹⁰⁰

⁹⁵ J. L. Wiebers and J. A. Shapiro, *Biochemistry* **16**, 1044 (1977).

⁹⁶ D. R. Burgard, S. P. Perone, and J. L. Wiebers, *Biochemistry* **16**, 1051 (1977).

⁹⁷ B. R. Kowalski, *Anal. Chem.* **47**, 1152A (1975); also see his previous papers on similar computer applications not related to the sequence of nucleic acids problem.

⁹⁸ G. Holzmann and G. Kostmehl, *Org. Mass Spectrom.* **15**, 336 (1980).

⁹⁹ R. D. Macfarlane, quotation taken from Ref. 5.

¹⁰⁰ C. J. McNeal, K. K. Ogilvie, N. Y. Theriault, and M. J. Nemer, *J. Am. Chem. Soc.* **104**, 976 (1982).

Fast-atom bombardment studies on polynucleotides have been reported by Grotjahn¹⁰¹ and ourselves.^{102,103} Early reports dealt with three FAB negative-ion (Xenon at 8 keV*, glycerol matrix) spectra of hexa-, octa-, and decaoxyribonucleotides where the highest mass observed was the $[M - 1]^-$ ion. Under these conditions polynucleotides undergo fragmentation from both the 5' and 3' ends. Thus two series of $[M - 1]^-$ ions can be isolated. In practice, the series starting from the 5' end is generally more intense than that from the 3' end. The sequence reads the same from both ends as expected. Other ion clusters are observed at higher masses. They have one peak more intense than the rest of the group, and this peak is usually assigned to a fragment consisting of $[M - 1]^-$ minus the first terminal (either 5' or 3') nucleoside. This is followed by sequential cleavages of the remaining nucleotides until the opposite end is reached.

For instance, 5'd(ApCpTpCpGpApTpG) 3' octanucleotide shows an $[M - 1]^-$ ion at m/z 2407 and fragments corresponding to $N_{n,p}$ and $N_{1,p}$ bond cleavages at m/z 2174 and 2158 confirming the identity of the end nucleosides. The sensitivity of the method has been established at two to four A260 units†. Using a similar technique, we have worked¹⁰³ with different glycerol-glyme matrices and achieved the sequence determination of the ammonium salt of a derivatized hexanucleotide sample at the subnanogram level‡. Using a simple sequence search simulation program, we have compared¹⁰² a theoretical spectrum of this hexanucleotide to the experimental one. In such a manner, an extremely fast sequence analysis could be accomplished; complete identification takes less than 5 min. Continuing this study by FAB negative-ion mass spectrometry with octa- and dodecaoxynucleotides¹⁰³ and some ribonucleotides, we have established a typical sequential fragmentation pattern similar to that presented in Table VI for both deoxyribo- and ribopolynucleotides.

The presence of terminal C and G in 5'd(CpTpGpApTpCpApG) 3' octanucleotide is supported by two sets of data: the presence of a 5' C terminal ion (very strong) at 306 and a 3' terminal G at 346 as well as a loss of 209 amu from the 3' end. The location of the next two nucleotides, T and A, is evidenced by the losses of (see column 2, Table VI) 304 and 313 amu,

¹⁰¹ L. Grotjahn, R. Frank, and H. Blocker, *Nucleic Acids Res.* **10**, 4671 (1982); *Int. J. Mass Spectrom. Ion Phys.* **46**, 439 (1983).

¹⁰² K. Jankowski and F. Soler, *Spectrosc. Int. J.* **4**, 35 (1985).

¹⁰³ K. Jankowski, Unpublished data (work in progress).

* Optimized at 9–9.5 keV.¹⁰²

† At 8 keV (minimum).

‡ Lyophilization of the sample is recommended (if not required) for the recording of any EI spectrum of a nucleic acid.

respectively; the sequence analysis can be continued, in either direction, up to the end.

A similar analysis can be accomplished on ribonucleotides as it can be concluded from the lower part of Table VI. Finally, a simulation of fragmentation, i.e., constructing a theoretical spectrum under FAB conditions, can be performed by simply inserting the base units, A, C, T, etc. into the possible sequence (the program starts from the 5' end) and then comparing to the experimental spectrum.

This method also suffers from mass limit restrictions, which for FAB is ~ 6000 amu with the definite probability of expanding these limits to the 12,500 amu range.¹⁰⁴ Instrumentation capable of such high mass analysis has not been used to date for the sequence analysis of polynucleotides.

For extended polynucleotides we proposed a half-sequence analysis, which, in principle, is very simple. Let us consider, for example, the 5' (ApGpGpApApApUpG) 3' octanucleotide, the partial sequence of which can be established from west (5' end) to east involving four plus one nucleotides (five) and from east (3' end) to west involving four plus one nucleotide fragments.¹⁰³ The complete sequence can be established by the computer, using all the intense ions only, as soon as the analysis reaches the overlapping central nucleotide sequence A – A.

A major advantage is the extension of the mass range to approximately double the actual mass limits, e.g., in the eicos–tetcos nucleotides ($n = 20–24$) range. This half-sequence method with the appropriate computer pro-

TABLE VI
IONS USED IN SEQUENCE ANALYSIS OF NUCLEOTIDES

Series of nucleotides		First cleavage from $M - 1^a$	Following cleavage ^b	Terminal ion
Deoxyribo	A	– 233	– 313	330
	C	– 209	– 289	306
	G	– 249	– 329	346
	T	– 224	– 304	321
Ribo	A	– 249	– 329	346
	C	– 225	– 305	322
	G	– 265	– 345	362
	U	– 226	– 306	323

^a Minus indicated mass.

^b Previous nucleotide ion mass minus indicated mass.

¹⁰⁴ K. L. Rinehart, Jr., *Science* **218**, 254 (1982).

gram is available from the authors.¹⁰³ The primary disadvantage in using our demi-sequence method for sequential analysis arises when the same partial sequence of two (or more), nucleotides occurs twice at a central position in the polynucleotide to be analyzed. In this situation, the program still gives a correct sequence from both sides but only up to the central part of the nucleotide; consequently, the nucleotide size will appear shorter. In the 5'd (CpTpGpApTpApTpCpApG) 3' decanucleotide, for example, the ApT sequence is present twice; in such a situation the data must be compared to the original spectrum for the higher mass ions. The analysis can then be confirmed by the aforementioned simulation, since sequences from both ends will be the correct ones.

One of the most challenging problems studied by our group¹⁰⁵ (Table VII) involved sequencing a dodecadeoxyribonucleotide (molecular mass of 3642 amu). For that nucleotide we have designed a special outline program, which provides a different type of sequential information. Let us consider, for instance, the structure of d5' (CpTpGpApTpGpCpApTpCpApG) 3'. All clusters are computer analyzed and fitted into a working scheme, using, as an additional criterion, the predominance of the intense ions over the weaker ones within the same cluster of ± 5 amu range. As a result, a series of "partial identifications" is obtained; we can read partial sequences of tri- and tetra-nucleotides, e.g., CpTpG and CpApG, TpGpApT, several dinucleotides sequences, and finally, a full sequence even though the spectrum shows a peak at m/z 3724 (82 amu greater than the molecular ion). It should be noted that the so-called full-sequence program, as opposed to the half-sequence

TABLE VII
FAB SPECTRUM OF A DODECADEOXYRIBONUCLEOTIDE

5' end		
[M - 1]	3642 CpTpGpApTpGpCpApTpCpApG	Cp 306
	3433 pTpGpApTpGpCpApTpCpApG	CpTp 610
	3129 pGpApTpGpCpApTpCpApG	CpTpGp 939
	2800 pApTpGpCpApTpCpApG	CpTpGpAp 1252
	2487 pTpGpCpApTpCpApG	CpTpGpApTp 1556
	2183 pGpCpApTpCpApG	CpTpGpApTpGp 1885
	1854 pCpApTpCpApG	CpTpGpApTpGpCp 2174
	1565 pApTpCpApG	CpTpGpApTpGpCpAp 2487
	1252 pTpCpApG	CpTpGpApTpGpCpApTp 2791
	948 pCpApG	CpTpGpApTpGpCpApTpCp 3000
	659 pApG	CpTpGpApTpGpCpApTpCpAp 3393
	346 pG	CpTpGpApTpGpCpApTpCpApG 3642 [M - 1]
		3' end

¹⁰⁵ K. Jankowski and F. Soler, *J. Bioelectr.* **3**, 299 (1984).

program, gives three possible solutions. One of these solutions is the exact sequence of the dodecanucleotide in question. This program allows the multiple use of the same mass, e.g., 1252 and 2487 are present twice in the sequence. Table VII illustrates the full sequential analysis of this dodecanucleotide. The sequence was performed on two to four A260 units in a few minutes, including the time involved in the recording of the spectrum, with a little help from the mass spectrometer operator.

As for any analytical technique, a major problem lies in the purity of the polynucleotide sample, although nucleoprotein contamination is not prohibitive to the recording of FAB spectra. Furthermore, it must be noted that branched polynucleotides cannot be analyzed with our programs, exception made of the fragmentary information obtained from all ends.

In spite of these apparent limitation, the sequencing of polynucleotides, using FAB mass spectrometry (that produces only a few intense ions), looks very promising. Fast-atom bombardment has not yet reached the molecular-weight level of native DNA or RNA, and the ultimate answer might lie around the use of new bombardment atoms or perhaps even around the resurgence of the almost abandoned time-of-flight spectrometers.

In order to prepare a suspension of polynucleotides or nucleic acids in a solvent (e.g., in glycerol) we have used a low-power, short-time (5–10 min) ultrasonification method, and although the ultrasonification could, in principle, have lead to complete disintegration of the sample, we found that these compounds remained stable and intact under our operating conditions. Stability tests do not show detectable modifications in either base structure or composition.

VII. Concluding Remarks

In spite of the incomplete coverage in classical reviews and the absence of references in chemical and biochemical texts on mass spectral studies applied to nucleic acids and their derivatives, mass spectrometry is a very promising technique for studying these compounds. The analysis of the relevant building blocks (nucleosides and nucleotides) is satisfactorily achieved, whereas the analysis of the polymers (oligonucleotides and nucleic acids) still needs refinement despite the sophistication level of the techniques used. The future looks very promising for the sequence analysis of nucleic acids and this, along with structural elucidation studies of modified bases, for example, could establish mass spectrometry as a routine technique in this area.

VIII. Addendum

The bibliography of this chapter covers the literature up to the beginning of 1983. In order to include some significant post-1983 findings, we would like to add two comments concerning (a) the mechanism of pyrolytic mass spectrometry (Py-MS) of oligonucleotides and (b) sequence analysis.^{1-5,7-33,37-48,76}

A. MECHANISM OF PY-MS OF OLIGONUCLEOTIDES

The controversy around the two possible origins of the BH ion (from direct pyrolysis or from the nucleoside-like ion) necessitated studies using linked scan techniques and metastable-ion mapping.¹⁰⁶ From those results it is clear that the BH ions, as well as methylfuran particles, are formed directly by the pyrolytic process.

The corresponding daughter-parent ion transitions were not detected (Fig. 25). These results have been further confirmed by Py-CI studies performed on the same ions, using ammonia (NH₃ and ND₃) as reagent gas.¹⁰⁷ More precise information about the binding of methylfuran moieties to the base ("the dot studies" in Wiebers's proposal⁷³) and about its nature have been obtained from SIM studies of pyrolytic spectra of DNA. The "dot" in Wiebers's scheme is of a covalent nature. Mass separation-mass spectroscopic experiments¹⁰⁸ confirmed the covalent nature of [BH + 160] and [BH + 240] ions. More precision about such bindings could be obtained only from carefully chosen model studies. In this series the bi- (or tri-) ribosynucleosides simply do not exist or are highly difficult to synthesize. The [BH + 160] ion is probably formed with the C-C or the ether bond between two furan moieties. The partial structure of this fragment (that follows) shows the C-3-C-4(O-)-C-5 unit. This fragmentation involves a butane-base fragment.¹⁹ The C-C bond between two methylfuran moieties agrees well with a polymerization of small heterocycles as well as with the well-known tail-head (or two other possibilities) or enolic ether couplings.² The study of the copolymer of deoxyribose DNA supports this hypothesis.¹⁰⁸

¹⁰⁶ K. Jankowski, D. Gaudin, and H. Virelizier, *Spectrosc. Lett.* **18**, 243 (1985).

¹⁰⁷ K. Jankowski, D. Gaudin, H. Virelizier and R. Hagemann, Unpublished data (work in progress).

¹⁰⁸ J. C. Tabet, K. Jankowski, and H. Virelizier, Unpublished data (work in progress).

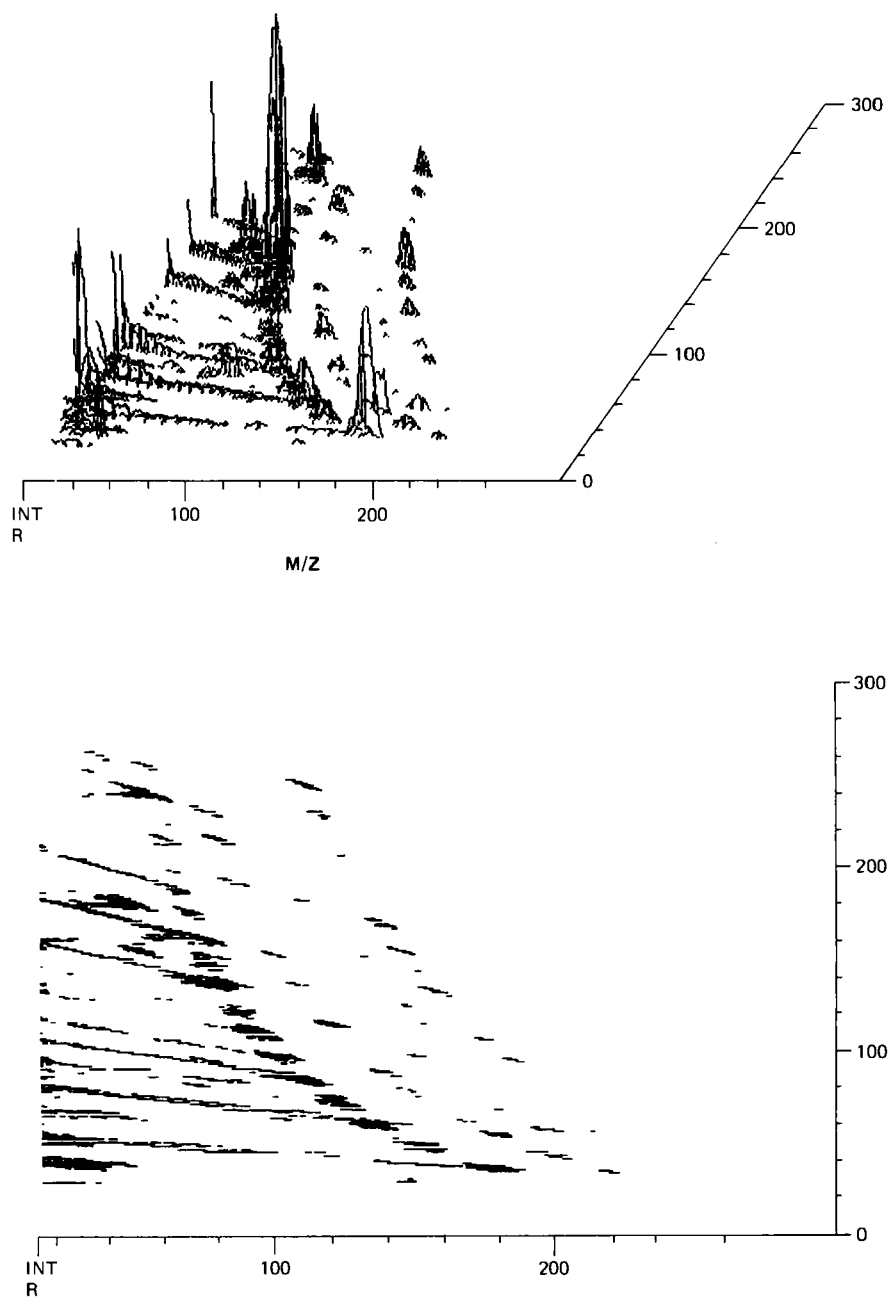


FIG. 25. DNA herring sperm; B/E map for the unimolecular decomposition of ions MS 80-DS 55.

B. SEQUENCE ANALYSIS

The progress in this area has been limited by two factors: the mass range actually attained in FAB and the quantity (and purity) of compounds available. The mass range has been expanded, using, for example, postacceleration to 6–10 kilodaltons (at ~ 8 kV); however, very few new and larger oligonucleotide spectra have been reported.

Grotjahn¹⁰⁹ has sequenced oligonucleotides, using NI–FAB. The spectra recorded in a glycerol matrix with 1.5 OD 260 (min) of synthetic material (protected or as the triethylammonium salt at 9–9.5 kV) show the sequence pattern.* Using a copper probe tip, we recorded spectra of mixed ribo- and deoxyribonucleotides in a mass range of less than 4000 daltons.¹¹¹ Another Canadian team¹¹² has studied di- to pentanucleotides by NI–FAB. The 5' and 3' cleavage discriminations observed by Grotjahn¹⁰¹ have not been confirmed for small nucleotides; this factor can affect and dramatically slow down the automatization of the sequence analysis by FAB–MS. As usual, the purity of compounds used could account for these phenomena—Grotjahn used primarily triethylammonium salts of oligonucleotides, whereas commercial or synthetic materials are usually mixtures of free phosphates and triethylammonium salts.

A new approach to the sequence analysis of polynucleotides in conjunction with the biosynthetic relation between peptide (protein) and the nucleotide fragments has been developed at MIT. Biemann¹¹³ and Costello¹¹⁴ introduced a mass spectrometric/biochemical technique for verifying a DNA sequence from the matching peptide sequence and the corresponding trios of nucleotides (and probably vice versa). For example, for glycine the base trio in the polynucleotide corresponds to the sequence C–A–G. This method, although slow and expensive, looks very promising. It is necessary to remark that, for example, a tridecapeptide corresponds to a 39-nucleotide chain, averaging a mass of $\sim 12,000$ daltons and possessing a unique sequence. The tridecapeptide mass range is no longer prohibitive for normal

¹⁰⁹ L. Grotjahn, R. Frank, and H. Blocker, *Proc. 31st Annu. Conf. Mass Spectrom. Allied Top.* 1983, p. 644.

¹¹⁰ F. McLafferty, to be published.

¹¹¹ K. Jankowski, R. Tulol, J. Ulrich, F. Soler, and D. Gaudin, *J. Bioelectr.* **4**, 43 (1985).

¹¹² A. M. Hogg, J. G. Velland, and J. C. Vedevas, *Proc. 31st Annu. Conf. Mass Spectrom. Allied Top.* 1983, p. 693.

¹¹³ B. W. Gibson, H. A. Scoble, and K. Biemann, *Proc. 31st Annu. Conf. Mass Spectrom. Allied Top.*, 1983, p. 640.

¹¹⁴ C. Costello, *Congr. Ann. ACFAS*, 51st, 1983.

* The maximum of sequence information has been obtained, according to McLafferty, at 9–9.5 keV.¹¹⁰

FAB study. Normally in this type of studies, the availability of material and the methodology used are the actual limitations. Additionally, they are subjected to a double-checking requirement for probable errors in the polynucleotide sequence determination. An interesting application of mass spectrometry to structural studies of synthetic DNA fragments has been developed by a team of German chemists. They monitored a solid-phase synthesis, step by step, from the very beginning by mass spectrometry; the data presented suggest that this might become a very attractive analytical application.¹¹⁵

ACKNOWLEDGMENTS

We would like to thank Drs. F. Söler, R. Hagemann, H. Virelizier, D. Gaudin, W. Guschlbauer, G. Simonnet, P. Fromageot, and J.-P. Macquet for their help in obtaining several samples and for their expert technical support. The authors would also like to express their gratitude for the indispensable contribution and the high degree of tolerance, understanding, and patience of both the Université de Moncton (Canada) and the Nuclear Research Center of Saclay (France). JRJP acknowledges the award of an NSERC-Canada Visiting Fellowship in Biotechnology.

¹¹⁵ L. Alder, A. Rosenthal, and D. Cech, *Nucleic Acids Res.* **11**, 843 (1983).

Chemistry of 8-Azapurines (1,2,3-Triazolo[4,5-*d*]pyrimidines)

ADRIEN ALBERT

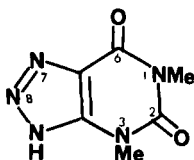
*Department of Chemistry, Faculty of Science, Australian National
University, Canberra, Australia 2601*

I. Introduction: Nomenclature, Tautomerism, Earlier Reviews, Databank	118
II. Structure and Physical Properties	121
A. Crystallography, Electron Density	121
B. Ionization in Water, Covalent Hydration	124
C. Ultraviolet Spectra	126
D. NMR Spectra	130
E. Infrared Spectra	131
F. Mass Spectra	132
G. Polarography and Miscellaneous	133
III. Reactivity	134
A. Reactivity of Ring Atoms	134
1. Electrophilic Attack on Nitrogen	134
2. Nucleophilic Attack on Carbon	138
3. Hydrogenation and Dehydrogenation	139
4. Dimerization, Analytical Determination, Photochemical Reactions	139
B. Reactivity of Substituents	140
1. Alkyl and Aralkyl Groups	141
2. Nitriles, Amides, Esters, and Related Groups	141
3. "Hydroxy" (Oxo) and Alkoxy Groups	142
4. Amino, Nitro, and Related Groups; <i>N</i> -Oxides	144
5. A Chloro Substituent	144
6. "Mercapto" (Thioxo), Methylthio, Methylsulfonyl, and Arylsulfonyl Groups	147
C. Ring Openings and Rearrangements	149
1. Ring Opening without Reclosure	149
2. Ring Opening with Spontaneous Reclosure	154
IV. Synthesis	156
A. Annulation of a Triazole Ring on to an Existing Pyrimidine Ring	156
B. Annulation of a Pyrimidine Ring on to an Existing Triazole Ring	160
1. From Rings with an Amino Group Adjacent to an Acid Amide, Thio- amide, or Ester Group	161
2. From Rings with an Amino Group Adjacent to a Nitrile, Amidine, or Aldehyde Group	165
3. From Rings with an Amino Group Adjacent to an Aminomethyl Group; Synthesis of 1,6-Dihydro-8-azapurines	168

C. Some Help in Choosing the Starting Materials	170
V. Biological and Industrial Applications	171
A. Investigations Aimed at the Treatment of Cancer	171
1. Studies in Mammals	172
2. Cell-Culture Studies	173
3. Biochemical Studies	174
4. Drug Resistance, Mutations	175
B. Investigations Aimed at Treating Allergies	176
C. Antiviral Studies	177
D. Miscellaneous Biological Investigations (Pharmacokinetics, Agriculture, Protection from Radiation)	178
E. Phototechnology	180

I. Introduction: Nomenclature, Tautomerism, Earlier Reviews, Databank

The first of the 8-azapurines, 1,3-dimethyl-8-azapurin-2,6-dione (**1**), was made at the start of this century by Wilhelm Traube,¹ who cyclized the corresponding 4,5-diaminopyrimidine with nitrous acid. Similar syntheses from pyrimidines, although excluding any possibility of placing an alkyl substituent in the 7 or 8 position, dominated the field until 1968 when appropriately substituted triazoles were introduced to overcome these limitations.^{2,3} These two approaches to the preparation of 8-azapurines, from pyrimidines or from triazoles, are expanded in Sections IV, A and B, respectively.



(1)

After Traube's initial work, very little 8-azapurine chemistry was recorded until 1945, when Richard Roblin and his colleagues in Connecticut made the 8-azapurine analogs of purines important in human metabolism, e.g., adenine, hypoxanthine, and guanine.⁴ These analogs were found to have strong biological (antipurine) activity (see Section V), and one of them (8-azaguanine) was soon adopted for treating cancer of the head and neck.

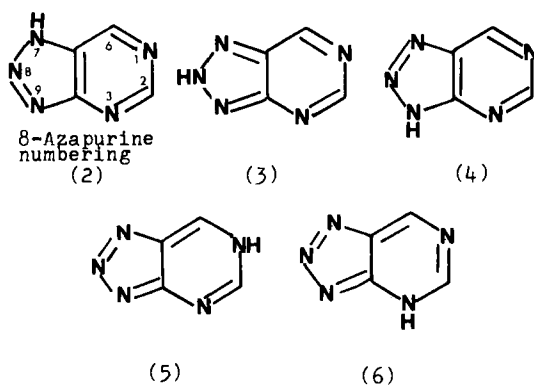
¹ W. Traube, *Ber. Dtsch. Chem. Ges.* **33**, 3056 (1900).

² A. Albert, *J. Chem. Soc. C*, 2076 (1968).

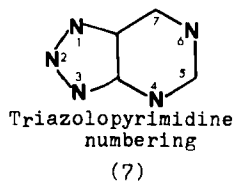
³ A. Albert and K. Tratt, *J. Chem. Soc. C*, 344 (1968).

⁴ R. O. Roblin, J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, *J. Am. Chem. Soc.* **67**, 290 (1945).

The mobile hydrogen atom in 8-azapurine can, theoretically, be attached to any one of the five nitrogen atoms, as in 2–6. Many analogs of 2–4, in which the hydrogen is replaced by a methyl group, are known, whereas similar analogs of 5 and 6 are uncommon,^{5,6} and, of these, 1-methyl-8-azapurine readily polymerizes.⁵ Although the bond arrangement in 3 may suggest instability, 8-methyl-8-azapurine remained unchanged² on long storage in air or when set aside for 20 h at 24°C in aqueous solution of pH 0–12. The proportions of tautomers in 8-azapurine are unknown, although those in 1,2,3-triazole have been ascertained by ¹H NMR (300 MHz) to vary with temperature, concentration, and solvent,⁷ and the proportions in 8-azapurine will probably also vary greatly according to conditions.



The name 8-azapurine, much used in chemistry and universally in biology, is short and self-explanatory. The full “replacement name” 1,2,3,4,6-pentaazaindene sometimes occurs in publications, and some editors prefer the “fusion name” [1*H*, 2*H*, or 3*H*]-1,2,3-triazolo[4,5-*d*]pyrimidine, which is also used by *Chemical Abstracts*. Some editors replace the 1,2,3 by *v*. When described as 8-azapurines (as will be done consistently on this review), the structures 2–6 (inclusive) are numbered as shown in 2. When described as triazolopyrimidines, structures 2–6 are numbered as in 7.



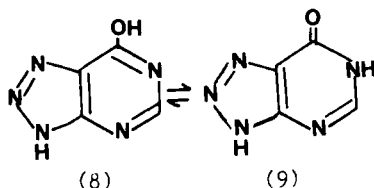
⁵ A. Albert, *J. C. S. Perkin I*, 513 (1978).

⁶ A. Albert, *J. C. S. Perkin I*, 2344 (1981).

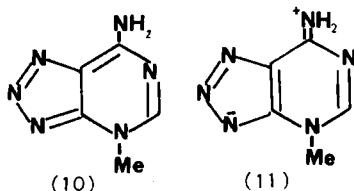
⁷ L. Lunazzi, F. Parisi, and D. Macciantelli, *J. C. S. Perkin II*, 1025 (1984).

The following abbreviations have become established in the biochemical literature: azaadenine (6-amino-8-azapurine), azahypoxanthine (8-azapurin-6-one), azaxanthine (8-azapurin-2,6-dione), azaguanine (2-amino-8-azapurin-6-one), azainosine (9- β -D-ribofuranosyl-8-azapurin-6-one).

C-Hydroxy-8-azapurines do not exist as such but as equilibrium mixtures (e.g., $8 \rightleftharpoons 9$) in which the cyclic amide tautomers greatly preponderate over the hydroxy tautomer.^{3,4} This behavior parallels what was found in the pyridine, pyrimidine, and purine series on evidence from ionization constants and the UV spectra of C- and N-methyl derivatives.^{8,9} A formal name for **9** is 1,6-dihydro-8-azapurin-6-one; but such specification of the hydrogen atom's position is, in the absence of data, risky: for example, pyrimidin-4-one is an equilibrium mixture in which tautomers with mobile hydrogen on N-3 and N-1 preponderate in a 5:2 ratio, respectively.⁹ Hence the simpler names, such as "8-azapurin-6-one," will be used in this review.



Primary amines in the 8-azapurine series present no evidence of any measurable proportion of imino-tautomer at equilibrium. An interesting variant is 6-amino-3-methyl-8-azapurine (**10**), which, like 6-amino-3-methylpurine,¹⁰ is a much weaker acid than the unmethylated analog.



The CAS ONLINE Databank of all 8-azapurines is accessible through the command: GRA R56, NOD 1 2 5 7 9N, BON ALL RU, RSPI. This yielded 1200 answers.

The 8-azapurines have previously been reviewed by Gut,¹¹ Robins,¹²

⁸ A. Albert and J. N. Phillips, *J. Chem. Soc. C*, 1294 (1956).

⁹ D. J. Brown, "The Pyrimidines," pp. 482, 494. Wiley (Interscience), New York, 1962.

¹⁰ B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 400 (1964).

¹¹ J. Gut, *Adv. Heterocycl. Chem.* **1**, 238 (1963).

¹² R. K. Robins, *Heterocycl. Compd.* **8**, 434 (1967).

Lunt,¹³ Shaw,¹⁴ and Schneller,¹⁵ in contributions of 13, 7, 6, 7, and 1 pages, respectively. The present review is intended as an extension of the one published in this series in 1963.¹¹ Early material has been included here briefly only where needed as a basis for describing further developments. Of these, the three most significant seem to be: ring opening, a great expansion of physical chemistry, and the increased use of triazoles as starting materials for synthesis, topics which other reviews cover insufficiently. Time, temperature, and yields of reactions will be recorded to help the synthesis chemist.

II. Structure and Physical Properties

A. CRYSTALLOGRAPHY, ELECTRON DENSITY

The two rings of 8-azapurine molecules are individually flat and, at least in the derivatives discussed in this section, inclined to one another at very small angles. Melting points are low and sharp in the absence of hydrogen-bonding structures such as NH_2 and (in the ring) CONH .

The simplest examples examined by X-ray diffraction are 6-amino-8-azapurine (azaadenine) hydrochloride (anhydrous),¹⁶ 6-amino-7-methyl-8-azapurine (anhydrous),¹⁷ and 8-azapurin-6-one (azahypoxanthine).¹⁸ In the last-named, the triazole ring proton is located entirely on N-8, and the proton from the (vinylogous) cyclic amide group is on N-3. 2,6-Diamino-8-azapurine sulfate (monohydrate) has the triazole proton on N-8 and the cationic proton on N-3.¹⁹ On the other hand, 2-amino-8-azapurin-6-one (azaguanine) (monohydrate)²⁰ bears the triazole proton on N-9 just as in guanine (monohydrate).²¹ 8-Azaguanine hydrochloride and hydrobromide (the latter is anhydrous) both²² carry protons on N-8, N-1, and on N-3, whereas the cation of guanine has these protons on N-9, N-7, and N-3, respectively.²³

¹³ E. Lunt, in "Comprehensive Organic Chemistry" (P. G. Sammes, ed.), Vol 4, p. 547. Pergamon, Oxford, 1979.

¹⁴ G. Shaw, in "Rodd's Chemistry of Carbon Compounds" (S. Coffey, ed.), 2nd ed., Vol. 4L, p. 109. Elsevier, Amsterdam, 1980.

¹⁵ S. W. Schneller, in "Comprehensive Heterocyclic Chemistry" (K. T. Potts, ed.), Vol. 5, p. 875. Pergamon, Oxford, 1984.

¹⁶ L. G. Purnell and D. J. Hodgson, *Acta Crystallogr., Part B* **B32**, 1450 (1976).

¹⁷ A. L. Shoemaker and D. J. Hodgson, *J. Am. Chem. Soc.* **99**, 4119 (1977).

¹⁸ P. Singh, D. L. Lewis, and D. J. Hodgson, *J. Cryst. Mol. Struct.* **4**, 263 (1974).

¹⁹ P. Singh and D. J. Hodgson, *Acta Crystallogr., Part B* **B31**, 845 (1975).

²⁰ J. Sletten, E. Sletten, and L. H. Jensen, *Acta Crystallogr., Part B* **B24**, 1692 (1968).

²¹ U. Thewalt, C. E. Bugg, and R. E. Marsh, *Acta Crystallogr., Part B* **B27**, 2358 (1971).

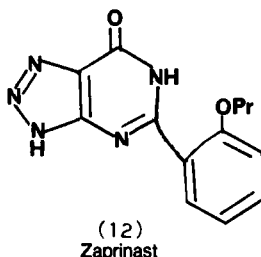
²² D. L. Kozlowski, P. Singh, and D. J. Hodgson, *Acta Crystallogr., Part B* **B31**, 1751 (1975).

²³ J. Broomhead, *Acta Crystallogr., Part B* **B4**, 92 (1951).

8-Azapurin-2,6-dione (azaxanthine) (monohydrate)²⁴ carries protons on N-8, N-3, and N-1, and 3-methyl-8-azaguanine hydrobromide (monohydrate) on N-8 and N-1.²⁵

The nucleoside 8-azaadenosine (monohydrate) was found to have a conformation intermediate between syn and anti (with a torsion angle of 104°) around the glycosyl – nitrogen bond, apparently stabilized by an electrostatic attraction between N-8 and C-2'. Adenosine deaminase, which can not deaminate any analogs with a syn conformation, has only a feeble action on this nucleoside.²⁶

Six derivatives of 2-phenyl-8-azapurin-6-one, which showed antiallergenic properties, have been examined.²⁷⁻²⁹ Because it is undergoing clinical trials, the most interesting of these is 2-(2-propoxyphenyl)-8-azapurin-6-one (12).³⁰ Although drug designers have shown that a massive structure in



the 2 position of 8-azapurin-6-one is necessary to elicit this biological effect, X-ray diffraction showed that this has caused no molecular distortion in 12. A strong intramolecular hydrogen bond that links N-1 with the ether oxygen atom, assists rigidity.²⁹ The crystallographic study of 8-methyl-2-phenyl-8-azapurin-6-one demonstrates the nonaromatic structure of a type-3 nucleus.²⁷

The crystal structure of *S*-8-azaadenosyl-L-homocysteine has been examined because this substance inhibits a methyltransferase that depends on *S*-adenosyl-L-methionine as a cofactor.³¹

²⁴ H. C. Mez and J. Donohoe, *Z. Kristallogr., Kristallgeom., Kristallphys., Kristallchem.* **130**, 376 (1969).

²⁵ P. Singh and D. J. Hodgson, *Acta Crystallogr., Part B* **B34**, 318 (1978).

²⁶ P. Singh and D. J. Hodgson, *J. Am. Chem. Soc.* **99**, 4807 (1977).

²⁷ S. J. Cline and D. J. Hodgson, *J. Am. Chem. Soc.* **102**, 6285 (1980).

²⁸ H. E. Le May and D. J. Hodgson, *J. Am. Chem. Soc.* **100**, 6474 (1978).

²⁹ S. R. Wilson, R. B. Wilson, A. L. Shoemaker, K. R. H. Wooldridge, and D. J. Hodgson, *J. Am. Chem. Soc.* **104**, 259 (1982).

³⁰ B. J. Broughton, P. Chaplen, P. Knowles, E. Lunt, S. Marshall, D. L. Pain, and K. R. H. Wooldridge, *J. Med. Chem.* **18**, 1117 (1975).

³¹ V. B. Pett, H.-S. Shieh, and H. M. Berman, *Acta Crystallogr., Part B* **B38**, 2611 (1982).

In all of the above crystal studies, bond lengths and bond angles were found to be similar to those of the corresponding purines. As with all X-ray diffraction work, it can not be assumed that a structure found in an anhydrous crystal would necessarily recur in a hydrated one (which, unfortunately, cannot always be obtained), nor do crystal studies necessarily reflect the tautomeric equilibrium attained in aqueous solution.

The crystallography of 8-azaadenine complexed with zinc³² and mercury³³ and of 8-azahypoxanthine with cadmium³⁴ and mercury³³ showed that the first two metals complexed with N-3 whereas the cadmium was bound to N-7. Cupric ions opened the nucleus of 8-azaadenine to give a triazole.³⁵

Quantum mechanical calculations of molecular orbitals have been performed on five examples (8-azapurine, -hypoxanthine, -guanine, -adenine, and -xanthine) by two methods: (a) a semiempirical approximation, which included contributions from the σ electrons of the skeleton, and (b) the CNDO approximation, which included contributions from all the valence electrons of the molecule.³⁶ The results were tabulated in parallel for each of the three possible positions of the triazole proton. In all 15 entries, the highest occupied and the lowest unoccupied molecular orbitals were calculated and also the dipole moment, the molecular energy, and the UV absorption maxima (the last-named showed only a modest agreement with experimental results). It was concluded that both types of calculation indicated that relative stabilities for the three tautomers (in each of the five sets) should decrease in the order HN-9, HN-7, and HN-8, and that the HN-8 tautomers should be 85 to 125 kJ (20–30 kcal) per mol less stable than the other two. However, it had to be admitted that, in all sets of three isomers examined experimentally, the HN-8 member has never been found inferior in stability.³⁶

Other calculations (CNDO/2) of the distribution of electrons in various 8-azapurines indicated that N-1 and N-3 (especially the latter) are by far the most electron rich (and hence the most basic) of the ring-nitrogen atoms; the negative charge on the three triazole nitrogen atoms is very small.^{17,26,29,30}

Calculation of electron densities of some 8-azapurines by a Hückel MO method successfully predicted NMR proton chemical shifts and the reactivity with nucleophiles but failed to predict the experimentally determined ionization constants.³⁷ Solid-state binding energies of 8-azaguanine and 8-

³² L. G. Purnell and D. J. Hodgson, *J. Am. Chem. Soc.* **99**, 3651 (1977).

³³ B. J. Graves and D. J. Hodgson, *Inorg. Chem.* **20**, 2223 (1981).

³⁴ L. G. Purnell, E. D. Estes, and D. J. Hodgson, *J. Am. Chem. Soc.* **98**, 740 (1976).

³⁵ L. G. Purnell, J. C. Shepherd, and D. J. Hodgson, *J. Am. Chem. Soc.* **97**, 2376 (1975).

³⁶ B. Pullman and A. Pullman, *Adv. Heterocycl. Chem.* **13**, 142 (1971).

³⁷ B. M. Lynch, A. J. Robertson, and J. G. K. Webb, *Can. J. Chem.* **47**, 1129 (1969).

azaxanthine, calculated from semiempirical, self-consistent electrostatic potentials and expressed as point charges, were found consistent with experimental data.³⁸ Perturbative configurational computations, using localized orbitals (PCILO), indicated that 8-azapurine nucleosides have conformations quite different from those of analogous purines. The calculations agreed well with NMR data but poorly with crystal structure.³⁹

The ionization energies of the charge-transfer complexes that 8-azaadenine and -guanine (electron donors) formed with chloranil were calculated from the UV absorption band. The results agreed with HOMO energies calculated by the Hückel method.⁴⁰ Other charge-transfer complexes of 8-azaguanine were studied.⁴¹

Magnetic circular dichroism of 9-methyl-8-azapurine and of 7-, 8-, and 9-methyl-8-azaadenine were better resolved than optical spectra and correlated well with CNDO calculations of absorption maxima; the calculated electron densities were also presented.⁴²

B. IONIZATION IN WATER, COVALENT HYDRATION

The ionization of 8-azapurines, which has not previously been reviewed, is complicated in many cases by covalent hydration, a phenomenon discovered by the present author in the pteridine and quinazoline series in 1952, and twice reviewed in this series.^{43,44} This occurrence of covalent hydration, which does not exist to any detectable degree in the purine series,^{45,46} indicates the increased π deficiency⁴⁷ conferred by the additional doubly bonded 8-nitrogen atom.

8-Azapurine has two pK_a values, an acidic one at 4.84 and a basic one at 2.05.⁴⁸ The former, compared to that (9.42) of 1,2,3-triazole,⁴⁹ reflects the acid-strengthening effect of the two doubly bonded nitrogen atoms in the pyrimidine ring. In the light of this electron-attracting influence, the basic

³⁸ Z. B. Maksic, K. Rupnik, and A. Veseli, *Z. Naturforsch.* **38A**, 866 (1983).

³⁹ A. Saran, C. Mitra, and B. Pullman, *Biochim. Biophys. Acta* **517**, 255 (1978).

⁴⁰ A. Fulton and L. E. Lyons, *Aust. J. Chem.* **21**, 419 (1968).

⁴¹ L. M. Korchevaya, *Biofizika* **16**, 928 (1971).

⁴² H. Weiler-Feilchenfeld, R. E. Lindner, G. Barth, E. Bunnenberg, and C. J. Djerassi, *Theor. Chim. Acta* **46**, 79 (1977).

⁴³ A. Albert and W. L. F. Armarego, *Adv. Heterocycl. Chem.* **4**, 1 (1965).

⁴⁴ A. Albert, *Adv. Heterocycl. Chem.* **20**, 117 (1976).

⁴⁵ J. W. Bunting and D. D. Perrin, *J. Chem. Soc. B*, 433 (1966).

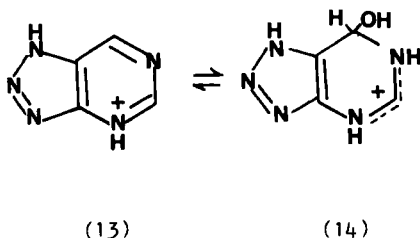
⁴⁶ A. Albert, *J. Chem. Soc. B*, 438 (1966).

⁴⁷ A. Albert, *Chem. Ind. (London)* 1171 (1953).

⁴⁸ A. Albert, *J. Chem. Soc. B*, 427 (1966).

⁴⁹ A. Albert, *Phys. Methods Heterocycl. Chem.* **1**, 98 (1963).

value (2.05) of 8-azapurine was seen to be anomalous compared to those of 1,2,3-triazole (1.17) and pyrimidine (1.31). More normal basic pK_a values were obtained for 9-methyl- and 6-methyl-8-azapurine (0.32 and 0.74, respectively) (cf. 1.25 for 1-methyl-1,2,3-triazole). These data pointed to the equilibrium $13 \rightleftharpoons 14$ as best representing the cation of 8-azapurine, whereas the neutral species and anion were shown to be virtually anhydrous.^{45,48} The choice of N-3 as the basic site followed from data given in Section III,A.



Ultraviolet and $^1\text{H-NMR}$ measurements supported these assignments. The UV absorption of 6- and 9-methyl-8-azapurine cations (which do not undergo detectable hydration) give the same values in anhydrous trifluoroacetic acid as they do in dilute hydrochloric acid. By contrast, the cations of 8-azapurine and its 1-, 2-, 7-, and 8-methyl derivatives have different UV spectra in these two solvents (a large shift of λ_{max} to shorter wavelengths occurs in the presence of water^{3,4,45}). This shift indicated conversion of a double bond to a single bond by hydration. Similarly the $^1\text{H-NMR}$ spectrum of the anhydrous cation showed peaks at δ 9.60 and 10.69 (for H-6 and H-2, respectively), whereas corresponding peaks for the hydrated cation (in D_2O , DCl) were at δ 6.81 and 8.54, respectively.⁴⁵

When the formation of the cation of 8-azapurine was observed (by UV) in a rapid-reaction apparatus, using solutions of increasing acidity, this cation was found to add water too fast for measurement. The more tractable 2-methyl-8-azapurine gave (by the same technique) a pK_a of 1.08, which, being the equilibrium between two totally anhydrous species, is termed⁴⁵ the "true anhydrous value" and forms a contrast with the "equilibrium" pK_a of 3.00 obtained in a 20-min potentiometric titration. It was calculated⁴⁵ from these results that the pK_a of anhydrous 8-azapurine is approximately zero.

The rapid-reaction method was used in reverse to obtain the true pK_a of hydrated 7-methyl-8-azapurine, which was 4.05 (cf. 1.92 for the value obtained by slow potentiometry).³ By contrast, the change from equilibrium titration to rapid-reaction technique raised the pK_a of 8-methyl-8-azapurine much less (from 3.18 to 4.2), which signifies much greater hydration (about 10%) in the neutral species.⁴ All of these hydrations were found to be first-order reactions, with $t_{0.5}$ varying from < 1 to 150 sec.

Prevention of hydration by the presence of a methyl group in the 6 position has been traced to a combination of both steric and electronic factors⁴⁴; most other substituents in the 6 position diminish hydration. It is not known why a methyl group in the 9 position of 8-azapurine decreases hydration. Substituents in the 2 position of 8-azapurines favor 1,6 hydration if they are mesomeric donors (+M) e.g., NH_2 or O; those that are inductive acceptors (−I) (e.g., SMe) oppose hydration by lowering the polarization of the 1,6 bond^{48,50} (cf. the similar responses of the 2 position in quinazolines⁵¹). The hydration of 8-azapurin-2-one stands apart from the above examples by being manifested mainly in the neutral species; the hydration of 8-azapurine-2-thione is barely detectable.

Some representative $\text{p}K_a$ values are presented in Table I. Other $\text{p}K_a$ values will be found in the references of that table^{2,3,45,48,58–62} and also in refs. 52–55. It can be seen from Table I that N-methylation of azapurin-6-one increases the acidic strength of the CONH ionization by eliminating the coulombic effect of the first ionization.

In studies of phase equilibria with heavy metals, formation constants have been determined for the 1:1 complexes that 8-azaadenine forms with Cu^{2+} , Ni^{2+} , Co^{2+} , and Mg^{2+} (in water at 30°C).⁵⁶ Similar studies⁵⁷ were made with 8-azaguanine and Be^{2+} , Ni^{2+} , Cu^{2+} , Pb^{2+} , Al^{3+} , Cr^{3+} , and UO_2^{6+} .

C. ULTRAVIOLET SPECTRA

Typical UV spectra of 8-azapurines show a prominent, rather featureless envelope with λ_{max} 255–275 nm ($\log \epsilon$ 3.8–4.0) and a second absorption area around 200 nm. Because substituting a pyridine-like nitrogen atom for carbon has little optical effect, the spectra of 8-azapurines usually resemble those of the corresponding purines, as Table II^{63,64} shows. To effect this

⁵⁰ A. Albert, *J. C. S. Perkin I*, 2918 (1980).

⁵¹ W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc. C*, 234 (1966).

⁵² T. Okano and M. Noji, *Yakugaku Zasshi* **88**, 434 (1968).

⁵³ A. Albert and H. Taguchi, *J. C. S. Perkin I*, 449 (1972).

⁵⁴ A. Albert, *J. C. S. Perkin I*, 461 (1972).

⁵⁵ A. Albert and A. M. Trotter, *J. C. S. Perkin I*, 992 (1979).

⁵⁶ R. Sridharan and C. R. Krishnamoorthy, *J. Coord. Chem.* **12**, 231 (1983).

⁵⁷ R. Nayan and A. K. Ray, *J. Indian Chem. Soc.* **54**, 759 (1977).

⁵⁸ B. Roth and J. Z. Strelitz, *J. Org. Chem.* **34**, 821 (1969).

⁵⁹ A. Albert, *J. Chem. Soc. C*, 152 (1969).

⁶⁰ G. Nübel and W. Pfeleiderer, *Chem. Ber.* **98**, 1060 (1965).

⁶¹ A. Albert, *J. C. S. Perkin I*, 291 (1976).

⁶² A. Albert and W. Pendergast, *J. C. S. Perkin I*, 457 (1972).

⁶³ A. Albert, in "Synthetic Procedures in Nucleic Acid Chemistry" (W. W. Zorbach and S. Tipson eds.), Vol. 2, pp. 1, 47. Wiley, New York, 1973.

⁶⁴ A. Albert, *J. C. S. Perkin I*, 2974 (1981).

TABLE I
REPRESENTATIVE IONIZATION CONSTANTS OF 8-AZAPURINES^e

Substance	pK _a		Reference
	As base	As acid	
8-Azapurine			
Unsubstituted	2.05 ^a	4.84	48
	~0.0 ^b		45
2-Methyl	3.00 ^a	5.28	45,48
	1.08 ^b		
6-Methyl	0.74 ^b	5.07	48
6,9-Dimethyl	0.71 ^b	—	48
7-Methyl	1.92 ^a	—	3
	4.05 ^c		
8-Methyl	3.18 ^a	—	2
	4.2 ^c		
9-Methyl	0.32 ^b	—	48
9-Benzyl	-0.05 ^b	—	48
2-Amino	2.50 ^a	6.46	45,48
	1.32 ^b		
	5.55 ^c		
2-Amino-6-methyl	1.97 ^b	6.58	48
6-Amino (8-azaadenine)	2.70 ^b	6.27	3
2,6-Diamino	3.68	7.58	58
2-Methylthio	-0.19 ^b	5.28	48
6-Hydrazino-8-methyl	4.15 ^b	—	2
8-Azapurin-2-one			
Unsubstituted	-1.61 ^c	6.51	45,48
		10.08	
6-Methyl	0.51 ^b	5.36	48
		10.66 ^d	
8-Azapurin-6-one			
Unsubstituted (8-azahypoxanthine)	-1.6	5.16	3
		10.78 ^d	
9-Methyl	—	8.06 ^d	59
2-Amino (8-Azaguanine)	1.04 ^b	6.54	48
8-Azapurine-2,6-dione			
Unsubstituted (8-azaxanthine)	—	4.66	60
		9.79	
7-Methyl	—	7.22	
9-Methyl	—	5.36	
1,3-Dimethyl	—	4.47	
8-Azapurine-2-thione			
Unsubstituted	—	4.80	48
6-Methyl	—	4.95	48
8-Azapurine-6-thione			
Unsubstituted	—	4.13	59
		9.44 ^d	
9-Methyl	—	7.21 ^d	59
1,6-Dihydro-8-azapurine			
Unsubstituted	5.65	8.92	48
7-Methyl	5.71	—	61
9-Benzyl	3.12	—	61
2-Hydroxy	-1.36	8.03	62
2-Mercapto	—	7.54	48
6-Imino-1-methyl	3.25	9.12	59

^a Equilibrium value. ^b True anhydrous pK_a. ^c True hydrated pK_a. ^d Ionization of CONH or COSH. ^e In water of 20°C.

TABLE II
COMPARISON OF THE UV SPECTRA OF 8-AZAPURINES AND PURINES^a

8-Azapurines	pH ^b	λ_{\max}	log ϵ	Purines	pH	λ_{\max}	log ϵ
8-Azapurine ⁴⁸				Purine			
A ^c	7.0	268	3.89	A	11.0	271	3.88
M	3.4	263	3.87	M	5.8	263	3.90
C ^d	0.0	248	3.91	C	0.4	260	3.79
6-Methyl-8-azapurine ⁴⁸				6-Methylpurine			
A	7.3	267	3.91	A	11.5	271	3.93
M	2.9	260	3.89	M	5.9	261	3.92
C	-1.5	260	3.85	C	0.0	265	3.88
9-Methyl-8-azapurine ⁴⁸				9-Methylpurine			
M	2.5	264	3.88	M	8.5	264	3.90
C	-2.0	263	3.73	C	0.6	263	3.77
8-Azahypoxanthine ³				Hypoxanthine			
A ^e	8.0	259	3.96	A ^e	10.4	258	4.05
M	2.0	253	3.94	M	5.2	249	4.02
C	-3.6	259	3.98	C	-0.8	248	4.02
8-Azaadenine ³				Adenine			
A	9.0	275	4.02	A	12.0	267	4.08
M	4.5	273	4.01	M	7.0	260	4.13
C	0.2	263	4.03	C	2.1	262	4.12
8-Azaguanine ⁴⁸				Guanine			
A ^e	8.8	244, 278	3.76, 3.79	A ^e	11.0	243, 273	3.93, 4.00
M	3.8	247, 266	4.05, 3.83	M	6.0	245, 274	4.04, 3.92
Azaxanthine ⁶⁰				Xanthine			
A ^e	7.0	265	3.93	A	10.0	241, 276	3.95, 3.97
M	2.0	263	3.81	M	5.0	225, 266	3.49, 4.03
1,6-dihydro-2-methyl-8-azapurine ⁴⁸				Dihydropurines ^f			
A	11.6	275	3.79				
Z ^g	7.8	276	3.75				
C	4.0	259	3.79				

^a References for 8-azapurines are in Table I. Purine spectra are from ref. 63, which contains many others, also pK_a values.

^b Because the pK_a values of 8-azapurines are lower than those of the corresponding purines, buffers of lower pH were used.

^c A = anion, M = molecule, C = cation.

^d Normal hydrated species.

^e Monoanion.

^f Zwitterion arising from high basic strength of N-1.

^g No exact analog exists, see ref. 64 for spectra of other 1,6-dihydropurines.

comparison among two families that differ so much in ionization constants, as these do, it is necessary to examine the spectra of single ionic species, which can be obtained in aqueous solution whose pH is at least 1.5 units distant from any pK_a value. Many other UV spectra can be traced from the pK references of Table I.

It is thought that purines owe their maximum in the 260-nm region to a polarized electronic transition in the direction C-2 \rightarrow C-4,⁶⁵ and 8-azapurines should behave similarly. However those ionic species of 8-azapurine that are subject to hydration exhibit (when compared to purines) a spectral shift of about 15–75 nm (to lower wavelengths) without loss of intensity.^{3,4,45,48}

TABLE III
¹H-NMR SPECTRA OF 8-AZAPURINES^f

Substituents	Species ^a	Solvent ^b	δ 2	δ 6	δ Me	References
None	M	D ₂ O	9.20	9.68	—	45
	C	TFA	9.60	10.31	—	45
	HC	DCI	8.54	6.81	—	45
1-Me	M	D ₂ O	9.12	9.79	4.43	5
	HC	DCI	8.50	6.61	3.57	5
2-Me	HC	DCI	—	6.71	2.62	45
6-Me	C	DCI	9.46	—	3.38	45
7-Me	M	D ₂ O	9.44	9.87	4.62	3,67
	C	TFA	9.87	10.55	4.90	3
	HC	DCI	8.68	7.05	4.28	3
8-Me	M	D ₂ O	9.18	9.69	4.75	2,67
	MH ^c	D ₂ O	7.44	6.43	—	2,67
	C	TFA ^d	—	—	—	2
	HC	DCI	8.44	6.65	4.19	2
9-Me	M	D ₂ O	9.47	9.89	4.48	3,67
	C	TFA	9.87	10.57	—	3
	C	DCI	9.58	10.11	—	3
2-NH ₂	M	DMSO	—	9.30	—	68
	C	TFA	—	9.68	—	45
	HC	DCI	—	6.49	—	45
1,6-H ₂	M	D ₂ O	— ^e	4.82 (2H)	—	48
	C	DCI	8.28	5.08 (2H)	—	48
1,6-H ₂ -7-Me	M	DMSO	6.92	4.77 (2H)	—	61

^a M = molecule, C = cation, H = hydrated.

^b TFA = anhydrous trifluoroacetic acid. DCI = *M* DCI in D₂O.

^c Both hydrated and anhydrous neutral species are present.

^d Decomposed by this solvent.

^e Signal is obscured by D₂O side bands.

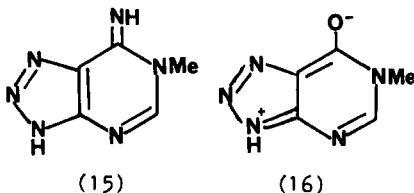
^f The assignment of peaks to H-2 and H-6 is as in ref. 66.

⁶⁵ S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

D. NMR SPECTRA

Some ^1H -NMR spectra of 8-azapurines (most often, those of the cations) are complicated by covalent hydration (Section II,B). Elucidation of these spectra has shed light on hydration in this series. The interpretations started with purine, which shows no sign of hydration.^{45,46} The pyrimidine ring of purine furnishes two singlet peaks (each 1H), at δ 8.82 (H-2) and 8.96 (H-6). Cation formation brings about the expected downfield shift⁴⁵ to 9.39 (H-2) and 9.56 (H-6).⁴⁵ Insertion of a nitrogen atom, to give 8-azapurine, shifted all of these signals downfield (see Table III),⁶⁶⁻⁶⁸ and in a consistent way so long as the cation was examined in an anhydrous solvent (e.g., trichloroacetic acid). However, when *M* DCl was substituted, a huge upfield shift appeared owing to saturation of the 1,6 double bond by hydration, which led to deshielding. Examination of the spectra of the monomethyl derivatives (Table III) shows that the 6 and 9 isomers resist hydration, whereas the 1, 2, 7, and 8 isomers are strongly hydrated when cationic, and the 8 isomer is also partly hydrated when molecular.

Other points of interest, illustrated in Table III, are the hydration of the cation of 2-amino-8-azapurine and the spectra of some 1,6-dihydro-azapurines. The spectra of substituted 1,6-dihydro-6-imino-1-methyl-8-azapurines (15) are similar to those of the isomeric 6-methylamino-8-azapurines to which they are readily converted, but only the latter show coupling (5 Hz) between protons of HNCH_3 .⁶⁹



Other ^1H -NMR spectra of simple 8-azapurines are in refs. 6, 50, 53-55, 62, 70, and 71 (glycosides), refs. 72-76 (*N*-benzyl), ref. 77 (dimer), refs. 78 and 79 (*N*-phenyl), and refs. 80-83.

⁶⁶ T. J. Batterham, "NMR Spectra of Simple Heterocycles," p. 301. Wiley, New York, 1973.

⁶⁷ A. Albert, W. Pfeleiderer, and D. Thacker, *J. Chem. Soc. C*, 1084 (1969).

⁶⁸ A. Albert and W. Pendergast, *J. C. S. Perkin I*, 1620 (1973).

⁶⁹ A. Albert, *J. C. S. Perkin I*, 2659 (1973).

⁷⁰ W. Hutzenlaub, R. L. Tolman, and R. K. Robins, *J. Med. Chem.* **15**, 879 (1972).

⁷¹ C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *J. Med. Chem.* **15**, 883 (1972).

⁷² A. Albert and D. Thacker, *J. C. S. Perkin I*, 468 (1972).

⁷³ J. D. Clayton, *J. Pharm. Sci.* **62**, 1432 (1973).

⁷⁴ A. Albert and W. Pendergast, *J. C. S. Perkin I*, 1625 (1973).

Proton and ^{31}P investigations of the glucosides 8-aza-5'- β -adenosine and -guanosine monophosphates, in water at pH 7, revealed conformations that differed markedly from those of the purine analogs.⁸⁴ Very few other non-proton NMR spectra have been published. The ^{13}C spectra of 8-azapurines, measured in aqueous alkali, show a downfield shift for C-2, C-5, and C-6 compared to their purine analogs, whereas C-4 signals show an upward shift.⁸⁵

E. INFRARED SPECTRA

In the 8-azapurine series, IR spectra have been used mainly to provide reference data for compound identification or to confirm the presence of an attached group. Most of the recorded spectra refer to the solid state for which almost identical results have been obtained in KBr disks and Nujol mulls. For some spectra obtained in solution, see ref. 3.

The parent substance, 8-azapurine, shows mainly "aromatic" bands, namely, at 1585, 1400, 1340, 1190, 980, and 800 cm^{-1} , plus NH-stretching bands at 3080 and 3000 cm^{-1} . In the 8-azapurinones ("hydroxy-8-azapurines"), the cyclic amide form (NHCO) is greatly favored at equilibrium over the tautomeric hydroxy form.³ Four absorption regions stand out clearly. The first of these consists of two or three NH-stretching bands near 3440, 3200, and 3100 cm^{-1} ; the others are bonds near 1700, 1600, and 1300 cm^{-1} , which correspond to the amide I, II, and III bands of Nakanishi.⁸⁶ These are attributed, respectively, to CO stretching, NH bending mixed with some CN stretching, and CN stretching mixed with some NH bending. For examples, see refs. 50, 55, and 76. All three bands are usually strong. Some rare cases are recorded where amide I is weaker than amide II.^{76,87} Little difference can be

⁷⁵ A. Albert, *J. C. S. Perkin I*, 2030 (1974).

⁷⁶ A. Albert, *J. C. S. Perkin I*, 345 (1975).

⁷⁷ T. Higashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.* **27**, 2431 (1979).

⁷⁸ T. Higashino, T. Katori, S. Yoshida, and E. Hayashi, *Chem. Pharm. Bull.* **27**, 2864 (1979).

⁷⁹ T. Higashino, T. Katori, H. Kawaraya, and E. Hayashi, *Chem. Pharm. Bull.* **28**, 337 (1980).

⁸⁰ A. Da Settimo, O. Livi, P. L. Ferrarini, and G. Primofiore, *Farmaco, Ed. Sci.* **35**, 298 (1980).

⁸¹ A. Da Settimo, O. Livi, P. L. Ferrarini, and G. Biagi, *Farmaco, Ed. Sci.* **35**, 308 (1980).

⁸² A. Albert, *J. C. S. Perkin I*, 887 (1981).

⁸³ T. Higashino, T. Katori, S. Yoshida, and E. Hayashi, *Chem. Pharm. Bull.* **28**, 255 (1980).

⁸⁴ C.-H. Lee, F. E. Evans, and R. H. Sarma, *J. Biol. Chem.*, **250**, 1290 (1975); H. D. Lüdemann, E. Westhof, and I. Cuno, *Z. Naturforsch., C: Biosci.* **31**, 135 (1976).

⁸⁵ L. G. Purnell and D. J. Hodgson, *Org. Magn. Reson.* **10**, 1 (1977).

⁸⁶ K. Nakanishi, "Infrared Absorption Spectrometry." Holden-Day, San Francisco, California, 1962.

⁸⁷ A. Albert, *J. C. S. Perkin I*, 2659 (1973).

seen between amide bands from 8-azapurin-6-ones, -2-ones, or -2,6-diones.⁵³

The IR spectrum of 1-methyl-8-azapurin-6-one differs remarkably from those of its 7-, 8-, and 9-methyl isomers by having strong absorption in the 2595-cm^{-1} region, which is particularly evident in a hexachlorobutadiene mull. It also has two peaks, at 1945 and 1815 cm^{-1} , which, although weak, are prominent because of the general lack of absorption in that area. Interestingly, two related substances, 9-benzyl-1-methyl- and 9-benzyl-1-butyl-8-azapurin-6-one, show absorption near 1950 cm^{-1} but not the other anomalies. In other ways, the spectrum of 1-methyl-8-azapurin-6-one closely resembles those of its three isomers; the extra absorption in the $2600\text{--}1800\text{-cm}^{-1}$ area is attributed to very strong hydrogen bonding caused by separation of charge, as in 16. Interestingly, the lower azalog, 1-methylpurin-6-one, has strong absorption in the $2800\text{--}2500\text{-cm}^{-1}$ region.⁵

The 8-azapurin-6-thiones ("mercapto-8-azapurines") often show strong CS-stretching bands near 1570 and some NH stretching near 3000 cm^{-1} .⁸⁸ Methylthio and methylsulfinyl groups give medium to strong bands in the $1190\text{--}1140\text{-cm}^{-1}$ region, and the methylsulfonyl group shows asymmetrical and symmetrical stretching around 1330 and 1140 cm^{-1} , respectively.⁵³ Other recorded bands include the C—Cl stretch near 800 cm^{-1} ,⁷⁶ the methoxy C—O—C stretch near 1230 s and 1030 m,⁵³ the amide and ester carbonyl stretch near 1700 ,⁸³ and the amidine (immonium) bending near 1950 cm^{-1} .⁸⁷ Many other infrared data are recorded in refs. 78–81. Some 6-cyano-8-azapurines do not absorb near 2200 cm^{-1} .⁷⁹

F. MASS SPECTRA

Although the mass spectrum of 8-azapurine is unrecorded, several of its 2- and 2,6-substituted derivatives have been examined.⁸⁹ The intensity of the molecular ion peaks, at the temperatures necessary to volatilize these substances (usually $200\text{--}300^\circ\text{C}$), testifies to the stability of the 8-azapurine skeleton. 8-Azaadenine underwent fragmentation by the loss of molecular nitrogen (from the triazole ring) followed by loss of two molecules (sequentially) of hydrogen cyanide. In a secondary fragmentation, the loss of N_2 was followed by that of H_2NCN . 8-Azahypoxanthine followed a similar route, by stepwise loss of N_2 , CO, and HCN. 2,6-Diamino-8-azapurine broke down simultaneously by two pathways: $\text{N}_2 + \text{HCN}$ and $\text{N}_2 + \text{H}_2\text{NCN}$. The base peak in the spectrum of 8-azaxanthine was not the molecular ion but a fragment of m/e 110. This peak arose from loss of HNCO from the molecu-

⁸⁸ A. Albert and C. Lin, *J. C. S. Perkin I*, 210 (1977).

⁸⁹ S. N. Bose, R. J. H. Davis, and D. R. Boyd, *Biomed. Mass Spectrom.* 4, 305 (1977).

lar ion by a retro-Diels–Alder fission, as happens with uracil and xanthine also. The m/e fragment then lost CO and N₂ in undetermined order. 8-Aza-adenine decomposes by several simultaneous processes. Interpretation of the mass spectra of these five 8-azapurines was supported by studies of metastable transitions, deuterium labeling, and accurate mass measurements.⁸⁹ The 1-, 3-, 7-monomethyl derivatives of 8-azaxanthine consecutively eliminated HCN, CO, and N₂.⁹⁰ For other mass spectra of 8-azapurines, see refs. 5, 55, 79, 83, and 91. *N*-Benzyl substituents readily furnish the fragment m/e 91.

A mass spectrum recorded for tris(trimethylsilyl)-8-azaguanine exemplifies the use of derivatization to increase volatility.⁹²

Many substances exhibit similar pathways of photochemical and electron-impact induced fragmentation. Hence this relationship may assist study of the photoproducts from 8-azapurines, which are more prone than purines to photodecomposition.⁹³

G. POLAROGRAPHY AND MISCELLANEOUS

In general, 8-azapurines are more easily reduced at the dropping mercury electrode than are the corresponding purines. The parent 8-azapurine gave half-wave potentials of -0.72 and -1.32 mV versus the standard calomel electrode, measured at pH 4.0 to avoid as much ionization as is possible (see Table I). This two-electron, two-step reduction, which produces 1,6-dihydro-8-azapurine, yields the relationship $E_{0.5} = -0.440 - 0.073\text{pH}$. 2-Amino-8-azapurine was equally easily reduced, whereas 6-amino-8-azapurine and 6-amino-8-azapurin-2-one proved more difficult; reduction of 2,6-diamino-8-azapurine halted at the one-electron step. The following 8-azapurines gave no reduction wave: 8-azapurin-6-one, 2-amino-8-azapurin-6-one, and 2-oxo-8-azapurin-6-one. In general, ease of reduction ran parallel to the energy levels of the lowest vacant orbitals as calculated by the simple LCAO method.⁵²

The octanol–water partition coefficients of 8-aza-adenine and -hypoxanthine (expressed as $\log P$) have been determined.⁹⁴

The stability constant of the adduct of 8-azaguanine with vitamin B-12a was determined in water at 25°C.⁹⁵

⁹⁰ S. K. Saha and W. Pfeleiderer, *Indian J. Chem., Sec. B* **19B**, 394 (1980).

⁹¹ Y. F. Shealy, J. D. Clayton, and C. A. O'Dell, *J. Heterocycl. Chem.* **10**, 601 (1973).

⁹² E. V. White and J. A. McCloskey, *Arch. Mass Spectral Data* **2**, 462 (1972).

⁹³ L. Kittler and H. Berg, *Photochem. Photobiol.* **6**, 199 (1967).

⁹⁴ A. Nahum and C. Horváth, *J. Chromatogr.* **192**, 315 (1980).

⁹⁵ K. Karo, F. Nome, and J. H. Fendler, *J. C. S. Dalton*, 1226 (1978).

III. Reactivity

In the 8-azapurines, the strong accumulation of π electrons by the ring-nitrogen atoms⁴⁷ makes the latter available for electrophilic attack, e.g., by alkylating agents. The corresponding deficiency of electrons on the ring-carbon atoms lays them open to nucleophilic attack. Nucleophilic exchange of substituents, by metathesis, plays a prominent part in 8-azapurine chemistry. The 8-azapurines are also very subject to ring opening, followed often by closure to a different substance.

A. REACTIVITY OF RING ATOMS

1. *Electrophilic Attack on Nitrogen*

The parent substance, 8-azapurine, was first prepared in 1957,⁹⁶ but its alkylation was not studied until 1969. Dimethyl sulfate in cold, aqueous sodium hydroxide (the pH held above 7) gave equal proportions of the 7-, 8-, and 9-methyl derivatives. These were separated by taking advantage of the lower basic strength of the 9 isomer (Table I), then proceeding by thin-layer chromatography.⁶⁷

Comparison of the pK_a values (Table I) of the first ionization constants of 8-azapurin-6-one (5.16) and its 9-methyl derivative (8.06) shows that the triazole proton is the more acidic. Hence alkylation under mildly alkaline conditions (monoanion) should favor the triazole ring. In agreement with this expectation, 8-azaxanthine (8-azapurin-2,6-dione) and dimethyl sulfate, stirred in dilute potassium hydroxide (40°C, 1 h), gave roughly equal proportions of the 7- and 8-monomethyl derivatives.⁹⁷ No 9-methyl-8-azaxanthine could be found. Earlier workers had isolated the 8-methyl isomer from a similar methylation by attempting to quaternize the crude product with methyl *p*-toluenesulfonate, an operation that left the sterically protected 8-methyl-azaxanthine unchanged (17% yield).⁶⁰ When the alkylation of 8-azaxanthine was repeated under more alkaline conditions, so that all of the starting material was present as the dianion, only 3-methyl-8-azaxanthine could be isolated (68% yield).⁹⁷

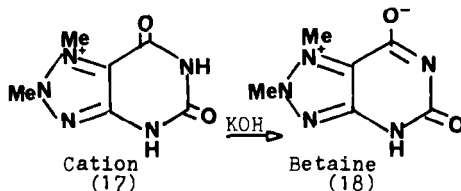
1-Methyl-, 3-methyl-, and 1,3-dimethyl-8-azaxanthine, methylated under mildly alkaline conditions, gave a mixture of the 7- and 8-methyl derivatives.⁹⁷ The 7- and 8-methyl-8-azaxanthines underwent alkylation on N-3,

⁹⁶ G. M. Timmis, D. G. I. Felton, H. O. J. Collier, and P. L. Huskinson, *J. Pharm. Pharmacol.* **9**, 46 (1957)[*CA* **51**, 10531 (1957)].

⁹⁷ N. V. Smirovna and M. B. Kolesova, *Zh. Org. Khim.* **14**, 1736 (1978); *J. Org. Chem. USSR (Engl. Transl.)* **14**, 1617 (1978).

but 9-methyl-8-azaxanthine proved unreactive.⁹⁷ Similar methylation of 1-methyl-8-azaxanthine gave 1,8-dimethyl-8-azaxanthine, whereas 3-methyl-8-azaxanthine produced a mixture of 3,7- and 3,8-dimethyl isomers.⁶⁰ Further methylation of 3,7- and 3,8-dimethyl-8-azaxanthines gave the 1,3,7- and 1,3,8-trimethyl analogs, respectively, of which the former was also obtained by the action of diazomethane on 1,3-dimethyl-8-azaxanthine.⁶⁰

Methylations with methyl arylsulfonates furnished quaternary salts of the type of 17, which were converted by cold, dilute alkali to betaines of type 18. Thus 8-methyl-8-azaxanthine and methyl benzenesulfonate (130°C, 3 h) gave 7,8-dimethyl-8-azaxanthinium benzenesulfonate (as 17), as well as the 7,9-dimethyl isomer, which arose through methyl migration. When 1,8-dimethyl-8-azaxanthine was treated similarly, the 1,7,8- and 1,8,9-trimethylated products were formed, whereas 3,8-dimethyl-8-azaxanthine gave only the 3,7,8-trimethylated product. Similar treatment of 1-methyl-, 3-methyl-, and 1,3-dimethyl-8-azaxanthine added two more methyl groups to each molecule, namely, in the 7 and 9 positions.⁹⁸ The migration of a methyl group from position 8 to 9 was favored by the use of methyl sulfate at 150°C. The slightly different alkylating action of methyl iodide was also studied.⁹⁸



Heating 8-azaxanthine with methyl *p*-toluenesulfonate (125°C, 2 h) gave the 7,9-dimethyl-8-azaxanthinium salt,⁹⁹ and 9-benzyl-8-azaxanthine similarly furnished the 9-benzyl-7-methyl analog.⁶⁰ 1,3-dimethyl-8-azaxanthine, when refluxed in dimethylformamide (1 h) with 6-azido-1,3-dimethyl-2,4-dioxypyrimidine, gave 9-(5-amino-1,3-dimethyl-2,4-dioxypyrimidin-6-yl)-1,3-dimethyl-8-azapurin-2,6-dione in 85% yield.¹⁰⁰

Interest in studying these alkylations of 8-azaxanthine was fueled by the desire to find practicable syntheses for 8-aza-theobromine, theophylline, and caffeine, and less work was done on the monooxo-8-azapurines. 9-Ben-

⁹⁸ M. B. Kolesova, Kh. L. Muravich-Alexandr, N. V. Smirovna, and M. Z. Girshovich, *Zh. Org. Khim.* **17**, 1080 (1981); *J. Org. Chem. USSR (Engl. Transl.)* **17**, 954 (1981).

⁹⁹ H. Bredereck and W. Baumann, *Justus Liebigs Ann. Chem.* **701**, 143 (1961).

¹⁰⁰ K. Hirota, K. Maruhashi, T. Asao, and S. Senoa, *Chem. Pharm. Bull.* **30**, 3377 (1982).

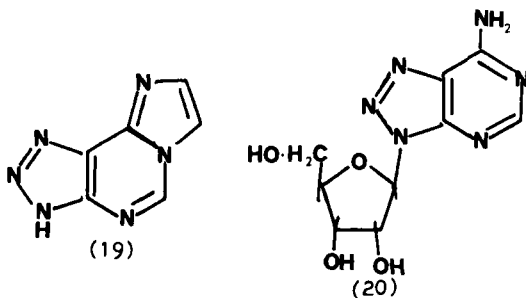
¹⁰¹ M. B. Kolesova and N. V. Smirovna, *Zh. Org. Khim.* **16**, 2204 (1980); *J. Org. Chem. USSR (Engl. Transl.)* **16**, 1879 (1980).

zyl-8-azapurin-6-one, iodomethane, and potassium carbonate, stirred in dimethylformamide (room temp., 1 day) gave a 94% yield of 9-benzyl-1-methyl-8-azapurin-6-one.⁵ The same azapurine and methyl *p*-toluenesulfonate gave 9-benzyl-7-methyl-8-azapurinium toluenesulfonate when heated in dimethylformamide (125°C, 2 h, 83% yield),⁹⁹ which dramatically indicates the versatility of a change of conditions.

Methylation of 8-azaadenine (6-amino-8-azapurine) with dimethyl sulfate in aqueous alkali gave a mixture of 3- and 9-methyl-8-azaadenine. The same starting material, with iodomethane in dimethylformamide (100°C, 1 h), gave 3,7-dimethyl-8-azaadeninium iodide in 75% yield. 9-Methyl-8-azaadenine similarly produced 1,9-dimethyl-8-azaadeninium iodide. Finally, 9-methyl-6-methylamino-8-azapurine, similarly treated, gave a mixture of the 1- and 7-methylated derivatives.¹⁰¹

Another type of N-alkylation is provided by the Mannich reaction. 1,3-Dimethyl-8-azapurin-2,6-dione, formaldehyde, and morpholine, stirred in cold ethanol, gave 1,3-dimethyl-7-(*N*-morpholinylmethyl)-8-azapurine-2,6-dione in 70% yield. Lower yields were obtained from piperidine and some piperazines.¹⁰²

Chloroacetaldehyde and 6-amino-8-azapurine, refluxed in sodium acetate solution, gave a tricyclic substance, imidazo[1,2-*c*][1,2,3]triazolo[4,5-*d*]pyrimidine (19).¹⁰³



6-Amino-8-azapurine 1-*N*-oxide was prepared by stirring 8-azaadenine with hydrogen peroxide in acetic acid at 25°C. (56% yield).¹⁰⁴

Glycosides. Because of their possible therapeutic value in acting as antagonists of the natural purine ribosides (nucleosides), interest remains high in attempts to improve yields of the 8-azapurin-9-β-*D*-ribosides, as well as analogs with other sugar residues.

¹⁰² D. S. Bariana and C. Groundwater, *J. Heterocycl. Chem.* **6**, 583 (1969).

¹⁰³ T. Sugimoto and S. Matsuura, *Bull. Chem. Soc. Jpn.* **50**, 1359 (1977).

¹⁰⁴ M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.* **82**, 3189 (1960).

These glycosides can be prepared by inserting the carbohydrate moiety into a suitable pyrimidine or triazole nucleus, followed by ring closure (see Section IV). However, the sugar residue is often introduced into a preformed 8-azapurine nucleus, and four principal methods are available. These may be termed the "sieves," "fusion," "mercuric," and "classic" methods.

The sieves method is exemplified by the refluxing, in benzene, of 6-methylthio-8-azapurine with 2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl 1-chloride and molecular sieves (Linde AW-500) (21 h). This gave a 2:1 ratio of the 9- and 8-triacetylribofuranosides of 6-methylthio-8-azapurine, separated on a silica column. Treatment with ammonia gave a 61% yield of pure 8-azaadenosine (20). The ratio of ribosides could be improved to 6:1 by an increase in time and temperature.¹⁰⁵ 2-Acetamido-6-methylthio-8-azapurine was ribosylated similarly.¹⁰⁶

Illustrative of the fusion method, 6-methylthio-8-azapurine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- α -D-arabinofuranose, when fused at 200°C, gave the 7-, 8-, and 9-arabinosides in 5, 24, and 37% yields, respectively.¹⁰⁷ A similar reaction to make the ribofuranoside benefited from the catalytic action of bis-*p*-nitrophenyl phosphate.⁷⁰ In an attempt to obtain the β anomer, 6-methylthio-8-azapurine and 2,3,5-tri-*O*-benzyl- β -D-arabinofuranosyl chloride were fused (120°C, 45 min). Even under these milder conditions, much anomerization to the unwanted α isomer occurred.¹⁰⁸ In a modification of the fusion reaction, tetra-*O*-acetyl-D-ribofuranose was heated with 6-nonanoylamino-8-azapurine to give azaadenosine in 14% yield.¹⁰⁹

Mercuric chloride, used to couple 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with 6-nonanoylamino-8-azaadenine, gave only the unwanted 8-riboside.¹¹⁰

In a modern silylated version of the classic approach, the tris(trimethylsilyl) derivative of 8-azaguanine, when stirred with 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl bromide in acetonitrile (at room temp.), yielded 35% of 8-azaguanosine.⁷⁰

In one of the few known attempts to prepare a deoxyriboside, 2-deoxy-3,5-di-*O*-*p*-tolyl-D-*erythro*-pentofuranosyl chloride and the silylated 8-azaguanine gave a mixture of both α and β anomers, of which the β has the

¹⁰⁵ J. A. Montgomery and R. D. Elliott, *Nucleic Acid Chem.* **2**, 687 (1978); *J. C. S. Chem. Commun.*, 1279 (1972).

¹⁰⁶ R. D. Elliott and J. A. Montgomery, *J. Med. Chem.* **19**, 1186 (1976).

¹⁰⁷ D. A. Baker, R. A. Harder, and R. L. Tolman, *J. C. S. Chem. Commun.*, 167 (1974).

¹⁰⁸ C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *J. Med. Chem.* **15**, 883 (1972).

¹⁰⁹ W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind. (London)*, 2007 (1963).

¹¹⁰ J. A. Montgomery, H. J. Thomas, and S. J. Clayton, *J. Heterocycl. Chem.* **7**, 215 (1970).

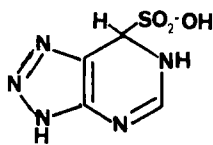
natural configuration.⁷⁰ Anomerization does not arise in the preparation of ordinary ribosides.

The removal of *N*-alkyl groups is described in Section III,B,1.

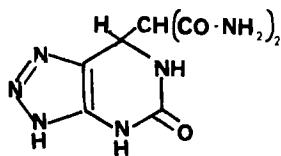
2. Nucleophilic Attack on Carbon

9-Methyl-8-azapurine, refluxed with methylmagnesium iodide in ether (3 h), gave 6,9-dimethyl-1,6-dihydro-8-azapurine in only 30% yield, but higher yields (up to 86%) were obtained with several homologous Grignard reagents. 9-Phenyl-8-azapurine, similarly alkylated in tetrahydrofuran, furnished 9-phenyl-6-alkyl-1,6-dihydro-8-azapurines in 71–86% yield.¹¹¹

The nucleophilic attack of water on the 1,6 position of 8-azapurines was dealt with in Sections II,B–D. Stronger nucleophiles were found to add more readily. Initially, the negatively charged atom of the nucleophile attacked the electron-deficient C-6 atom of the azapurine ring, and the reaction was completed by the addition of a hydrogen atom to N-1. Thus, the parent molecule, 8-azapurine, added methanol, benzenethiol, barbituric and thio-barbituric acids, and potassium hydrogen sulfite to give, respectively, 6-methoxy, 6-phenylthio, 6-(2,4,6-trioxohexahydropyrimidin-5-yl), 6-(4,6-dioxo-2-thioxohexahydropyrimidin-5-yl), and 6-sulfonato (**21**) derivatives of 1,6-dihydro-8-azapurine.⁶²



(21)



(22)

8-Azapurin-2-one gave similar adducts with all of the above reagents and also with acetylacetone, ethyl acetoacetate, diethyl malonate, and malonamide. The last-named Michael reagent furnished 6-dicarbamoylmethyl-1,6-dihydro-8-azapurin-2-one (**22**).⁶² Similar adducts were given by 2-amino-8-azapurine and 8-azapurine-2-thione. In general, the reactions took place rapidly, in cold aqueous solution, and yields ranged from 45 to 80%. However, methanol, a much weaker nucleophile, required 4 days' refluxing.⁶²

The oxidation of 8-azapurines to 8-azapurin-6-ones is derived from the preexisting 1,6 hydration (Section II,B). Thus the parent substance, set aside with 1 equiv of 30% hydrogen peroxide in *N* sulfuric acid (25°C, 4 days) gave 8-azapurin-6-one in 65% yield, and 2-amino-8-azapurine similarly fur-

¹¹¹ T. Higashino, T. Katori, S. Yoshida, and E. Hayashi, *Chem. Pharm. Bull.* **27**, 3176 (1979).

nished 2-amino-8-azapurin-6-one (80% yield).⁴⁸ Analogous results were obtained from 7-methyl-³ and 8-methyl-8-azapurine.² Iodine in aqueous sodium bicarbonate was used to oxidize 8-azapurin-2-one to 8-azapurine-2,6-dione in 50% yield (70°C, 6 h).⁴⁸

With more vigorously reacting nucleophiles, such as malononitrile, hydroxylamine, and hydrazines, the 1,2-addition reactions are often followed by ring opening, as described in Section III.C.

3. *Hydrogenation and Dehydrogenation*

8-Azapurines are easily reduced to 1,6-dihydro derivatives unless the 6 position is blocked. When both 3 and 6 positions are blocked, 1,2-hydrogenation can take place. No higher states of hydrogenation have been reported.

Sodium borohydride in 0.1 *N* sodium hydroxide (overnight at room temp) has proved a convenient reagent, as in the 1,6 hydrogenation of 8-azapurin-2-one⁶² and -2-thione⁴⁸ (both examples in 80% yield). Hydrogen gas over Raney nickel (atmospheric temp and pressure) was used for the 1,6 hydrogenation of 8-azapurine and 2-methyl-8-azapurine, the latter reduction being quantitative. Similarly, hydrogen over palladium reduced 3-methyl-8-azapurin-6-one to the 1,2-dihydro derivative at room temp (50% yield). The same reagents, in 3 *M* ethanolic ammonia at 75°C, converted 9-benzyl-3-methyl-8-azapurin-6-one to its 1,2-dihydro derivative (75% yield).⁶

a. *Dehydrogenations.* For removing two hydrogen atoms from dihydro-8-azapurines, manganese derivatives have been most used. Thus potassium permanganate, in water for aqua-soluble substrates, in aqueous potassium hydroxide for acidic substrates (azapurinones), or in aqueous pyridine or dimethylformamide, has given 75–90% yields of the dehydrogenated product.^{50,61} Equally successful was commercial precipitated manganese dioxide, in benzene or chloroform.^{61,82} A methylthio group, when present, was not affected.⁸²

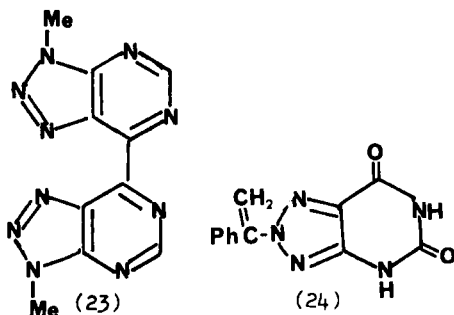
Potassium ferricyanide has been used in an emulsion of benzene and 2 *N* potassium hydroxide (room temp, 30 min) for the dehydrogenation of 8-benzyl-1,6-dihydro-8-azapurine⁷² (other examples in ref. 111).

4. *Dimerization, Analytical Determination, Photochemical Reactions*

9-Methyl-8-azapurine and potassium cyanide, set aside in water (room temp, 40 min), deposited crystals of the dimer 6,6'-bis-9-methyl-8-azapurine

(23) in 83% yield. This reaction, which began with nucleophilic addition of HCN to the 1,6 position, was completed by a benzoin-like condensation and final air oxidation. 9-Phenyl-8-azapurine was similarly dimerized in dimethyl sulfoxide.⁷⁷

8-Azaguanine and 8-azaxanthine were determined analytically in biological specimens by measuring the intensity of yellow color produced by cyanogen bromide.¹¹²



On irradiation with a high-pressure mercury lamp, 9-phenyl-8-azapurine in dioxane gave 9*H*-pyrimido[4,5-*b*]indole in 33% yield, whereas 54% was obtained in methanol. Nine derivatives of this azapurine, carrying various substituents in the 6 position, behaved similarly (32–91% yields). The principal by-products arose from (1) replacement of hydrogen in the 4 position of the pyrimidoindole by dioxane or methanol residues, (2) reaction with benzene, when used as a solvent, to yield 4-anilino-5-phenylpyrimidine, and (3) reaction with dioxane to furnish 4-anilinopyrimidines.¹¹³

1,3,7-Trimethyl-8-azapurine-2,4-dione, irradiated with diethylamine in acetonitrile, gave 6-diethylamino-1,2-dimethyl-5-methylaminopyrimidine-2,4-dione (66% yield). However, photolysis in methanol gave 5-hydroxy-1,3-dimethyl-6-methoxypyrimidine-2,4-dione (22% yield).¹¹⁴

B. REACTIVITY OF SUBSTITUENTS

Substituents attached to the carbon atom of 8-azapurines are activated much as the methyl group is in 2,4-dinitrotoluene. This has favored many metathetical exchanges of groups in the 6 position, which, because of the π

¹¹² L. D. Saslaw, N. A. Chaney, and V. S. Waraudekar, *Anal. Biochem.* **21**, 149 (1967).

¹¹³ T. Higashino, E. Hayashi, H. Matsuda, and T. Katori, *Heterocycles* **15**, 484 (1981).

¹¹⁴ I. Saito, S. Ito, H. Sugiyama, M. Akita, and T. Matsuura, *Tetrahedron Lett.*, 4065 (1979).

deficiency conferred by the extra nitrogen atom, is much more activated than in purine (but less so than the corresponding 4 position in pteridine). Very little is recorded about metathesis in the 2 position, probably because the requisite nucleophilic reagents could, alternatively, add across the 1,6 double bond. This type of difficulty has been encountered, and solved, in the pteridine series.¹¹⁵

1. *Alkyl and Aralkyl Groups*

The ring closure of 4,5-diamino-6-methylpyrimidin-2-one with sodium nitrite in cold, dilute acetic acid was slow enough (2 days) for nitrous acid to react with the 6-methyl-8-azapurin-2-one to give 6-hydroximino-8-azapurin-2-one. Replacement of acetic by hydrochloric acid accelerated the cyclization, and 6-methyl-8-azapurin-2-one was produced in 75% yield.⁴⁸

6-Amino-8-methyl-2-trichloromethyl-8-azapurine and tin(II) dichloride (in acetone at room temp, 18 h) gave a 66% yield of 6-amino-2-dichloromethyl-8-methyl-8-azapurine.⁷⁶

An *N*-benzyl group, inserted for protection, has usually been removed by stirring in liquid ammonia while sodium chips were added until a blue color persisted. Thus 9-benzyl-1,6-dihydro-6-imino-1-methyl-8-azapurine furnished 1,6-dihydro-6-imino-1-methyl-8-azapurine,⁸⁷ and 9-benzyl-6-butylamino-8-azapurine gave 6-butylamino-8-azapurine in 75% yield.⁷⁵ Hydrogenation over palladium was used to debenzylate 9-benzyl-7-methyl-2,6-dioxo-8-azapurinium betaine (similar to **18**) at 45°C.⁶⁰ 9-Benzyl-1-methyl-8-azapurin-6-one resisted all of these conditions, but hydrogenation over palladium in butanol-acetic acid at 117°C provided a 72% yield of 1-methyl-8-azapurin-6-one.⁵

The loss of a methyl group when polymethylated 8-azaxanthines were refluxed in pyridine has been briefly noted.⁹⁸

1,3-Dimethyl-8-(1-phenylvinyl)-8-azapurine-2,6-dione (**24**), refluxed for 10 h in formic acid, gave a 67% yield of 1,3-dimethyl-8-azapurine-2,6-dione.¹¹⁶

2. *Nitriles, Amides, Esters, and Related Groups*

6-Cyanopurines reacted readily with nucleophiles, of which two kinds were distinguished: some of these led to addition across the C≡N bond, whereas others simply replaced the cyano group.

¹¹⁵ J. Clark, *J. Chem. Soc.*, 4920 (1964); A. Albert and J. Clark, *ibid.*, 27 (1965).

¹¹⁶ K. Senga, Y. Kanamori, S. Nishigaki, and F. Yoneda, *Chem. Pharm. Bull.* **24**, 1917 (1976).

Of the first type of reagent, 98% sulfuric acid converted 6-cyano-9-phenyl-8-azapurine to the 6-carboxamide in 92% yield. The same azapurine, stirred with hydroxylamine hydrochloride and potassium carbonate in benzene-methanol (room temp, 3 h), gave 9-phenyl-8-azapurine-6-carboxamidoxime in 96% yield.⁸³

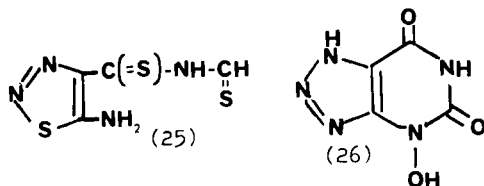
The second type of reaction was effected by amines, alkoxides, and the Michael and Grignard reagents. Thus 6-cyano-9-phenyl-8-azapurine reacted with methylamine to give 6-methylamino-9-phenyl-8-azapurine; ammonia, butylamine, benzylamine, aniline, diethylamine, and piperidine reacted similarly to give a 70–88% yield in benzene (25–80°C, 5–90 min). Again, refluxing methanolic sodium methoxide produced 6-methoxy-9-phenyl-8-azapurine; the alkoxides of ethanol, isopropanol, and benzyl alcohol reacted similarly (2–60 min) in 60–90% yields. Acetone, in dimethylformamide (room temp, 30 min), furnished 6-acetonyl-9-phenyl-8-azapurine, and a similar reaction was given by diethyl malonate, ethyl acetoacetate, acetonitrile, and acetylacetone (yields 33–75%). Finally, Grignard reagents, when refluxed in tetrahydrofuran (2 h), replaced the cyano by an alkyl group, but in only feeble yields.⁸³

Usually, it is not easy to turn an amide into the corresponding ester, but 9-phenyl-8-azapurine-6-carboxamide, methanol, and sulfuric acid, refluxed for 3 h, gave methyl 9-phenyl-8-azapurine-6-carboxylate in 64% yield. The ethyl ester, made similarly, when stirred with ethanolic potassium hydroxide (room temp, 30 min), gave the carboxylic acid in 98% yield. The same ethyl ester, heated with hexylamine (60°C, 15 min), gave an 81% yield of the hexylamide; aniline reacted similarly when stirred (room temp, 24 h) with sodium hydride in dimethylformamide. The ethyl ester also reacted with hydroxylamine and some hydrazines to give the expected products (23–60% yields).⁸³

3. "Hydroxy" (Oxo) and Alkoxy Groups

Several conversions of the 6-oxo to the 6-thioxo functions by phosphorus pentasulfide have been recorded. The importance of a pure, sublimed reagent was emphasized.^{2,3,6} 3-Methyl-8-azapurin-6-one, stirred at the critical temperature of 85°C (45 min), gave a 50% yield of 3-methyl-8-azapurine-6-thione plus 25% of a totally unexpected product, 5-amino-1,2,3-thiadiazole-4-(*N*-thioformyl) carbothioamide (25).⁶ 1-Methyl-8-azapurin-6-one, another starting material with seemingly no labile hydrogen in the pyrimidine ring, furnished an 83% yield of 1-methyl-8-azapurine-6-thione. In general, when the 9 position bears a hydrogen atom or an alkyl or aryl group, the product is a thiadiazole (Section III,C), and an alkaline treatment is neces-

sary to obtain the required 8-azapurine-6-thione. The presence of 7- or 8-alkyl substituents in the starting material, however, favors the direct reaction.



Thus 8-benzyl- and 8-methyl-8-azapurin-6-one and phosphorus pentasulfide, when refluxed in pyridine (1 h), gave the required thione (82% yield).^{2,7} 2-Mercapto-8-methyl-8-azapurin-6-one, refluxed with phosphorus pentasulfide in pyridine (5 h), gave an 85% yield of the 2,6-dithione, and the 7-methyl isomer behaved likewise.⁵³

Conditions for the replacement of the oxo function by a chlorine atom were found to be critical, varying greatly for seemingly related starting materials. The least complicated case, 9-benzyl-8-azapurin-6-one, refluxed in phosphoryl chloride alone (1 h), gave a 51% yield of 9-benzyl-6-chloro-8-azapurine.⁵⁹ 9-Methyl-8-azapurin-6-one, refluxed with thionyl chloride and dimethylformamide in chloroform, furnished 6-chloro-9-methyl-8-azapurine in 71% yield, but these conditions did not improve the above yield of the 9-benzyl analog.⁵⁹ Diethylaniline was a necessary addition for the reaction of phosphoryl chloride with 7-methyl-8-azapurin-6-one (75% yield),³ but this mixture (or phosphoryl chloride alone) failed with the 9-methyl isomer⁵⁹ and proved erratic with the 8-methyl isomer for which the above thionyl chloride method succeeded.²

6-Chloro-8-azapurine, could not be prepared from 8-azapurin-6-one and phosphoryl chloride, even with the addition of dimethylaniline,¹¹⁷ but 9-phenyl-8-azapurin-6-one, refluxed with diethylaniline and phosphoryl chloride (2 h) produced 6-chloro-9-phenyl-8-azapurine in 65% yield,¹¹⁸ and 8-methyl-8-azapurine-2,6-dione, similarly treated, gave a 55% yield of 2,6-dichloro-8-methyl-8-azapurine.⁵³

The frequently required conversion of an oxo to an amino group has not been effected directly but through the 6-chloro or 6-methythio derivative (Sections III,B,5 and 6).

The literature of 8-azapurines records very few reactions of a group in the 2 position. However, 9-benzyl-2-ethoxy-8-azapurine, heated in ethanolic ammonia (180°C, 48 h), gave 2-amino-9-benzyl-8-azapurine (43% yield); also

¹¹⁷ H. Ballweg, *Justus Liebigs Ann. Chem.* **657**, 141 (1962).

¹¹⁸ D. J. Brown and M. Paddon-Row, *J. Chem. Soc. C*, 1856 (1967).

this ethoxy compound, heated with pyridine hydrochloride (no solvent, 135°C, 30 min), gave 9-benzyl-8-azapurin-2-one (60% yield).¹¹⁹

4. *Amino, Nitro, and Related Groups; N-Oxides*

Few N-acylations have been reported, but the 2-amino group in 8-azaguanine was acylated with decanoyl and tridecanoyl chloride.¹²⁰ A rare example of the exchange of an amino group for fluorine was the reaction of 2,6-diamino-8-azapurine 9-riboside with potassium nitrite and dilute fluoroboric acid (5°C, 1 h). Only the 2-amino group was replaced (21% yield).¹²¹

The conversion of a primary amino group to the oxo function is exemplified by the reaction of 2-amino-8-azapurin-6-one with sodium nitrite and dilute sulfuric acid at 65°C, which gave 8-azapurine-2,6-dione in 74% yield.^{4,122} To avoid racemization, 8-azapurine ribosides are preferably treated with barium nitrite and dilute acetic acid at room temperature (5 h); thus 8-azaguanosine gave a 59% yield of optically unaltered 8-azaxanthine.⁷⁰

Replacement of a hydrazino substituent by a hydrogen atom, the last stage in deoxygenating an 8-azapurin-6-one, has been effected with silver oxide in boiling 1-methylpropan-1-ol (1 h). Thus 6-hydrazino-9-methyl-8-azapurine gave 9-methyl-8-azapurine in 60% yield. Primary alcohols had to be avoided because of their tendency to add across the 1,6 position.^{2,59}

3-Hydroxy-8-azaxanthine (**26**), the tautomer of an *N*-oxide, when stirred with acetic anhydride (40°C, 40 min), yielded 3-acetoxy-7-acetyl-8-azaxanthine, which, set aside in methanol at room temperature (1 h), gave a 97% yield of 3-acetoxy-8-azaxanthine.¹²³ The *N*-oxide substituent of 2,6-dioxo-8-azapurine 3-oxide was removed by hydrogen over platinum (5 days).^{123a}

5. *A Chloro Substituent*

The 6-chloro-8-azapurines have been much used in exchange reactions, although they tend to decompose on storage and to incur wastage by hydrolysis while the desired nucleophilic replacement is being attempted. The methylthio analogs (Section III,B,6) are more stable and often perform bet-

¹¹⁹ A. Albert and H. Taguchi, *J. C. S. Perkin I*, 2037 (1973).

¹²⁰ A. Colautti, V. Maurich, and F. Rubessa, *Farmaco, Ed. Sci.* **26**, 710 (1971).

¹²¹ J. A. Montgomery, A. T. Shortnacy, and J. A. Secrist, *J. Med. Chem.* **26**, 1483 (1983).

¹²² H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.* **81**, 3046 (1959).

¹²³ N. J. M. Birdsall, T.-C. Lee, and W. Wölcke, *Tetrahedron* **27**, 5961 (1971).

^{123a} R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.* **30**, 408 (1965).

ter in these exchange reactions, but they require at least one more stage to synthesize.

a. *Dehalogenation.* Dehalogenation has been little explored, but 6-chloro-9-phenyl-8-azapurine, hydrogenated over palladium and magnesium oxide, in a mixture of benzene and water at room temperature, gave 9-phenyl-8-azapurine (70% yield). It was confirmed by MS that this product was not the expected 1,6-dihydro compound.⁷⁷

b. *Hydrolysis.* By boiling 2-amino-6-chloro-8-azapurine with aqueous sodium hydroxide (25 min), 2-amino-8-azapurin-6-one was formed in 96% yield,¹²⁴ but a related compound required 7 h.¹²⁵ Hydrolysis is quicker with dilute acid, but not always so clean.¹²⁶ The more difficult case of converting an imino to an oxo group, as in 6-imino-1, 6-dihydro-8-azapurine, has been accomplished by adding sodium nitrite to an acidified solution at 75°C (83% yield).^{126a}

c. *Conversion to Alkoxy Derivatives.* 6-Chloro-8-azapurine, refluxed for 10 min with a solution of sodium in methanol, ethanol, propanol, or butanol, formed the corresponding 6-alkoxy derivative in 80–85% yield,¹¹⁷ and many similar examples are recorded.^{2,3,59} Benzene, as solvent, assisted similar reactions with phenol and benzyl alcohol.^{79,127} Surprisingly, 2,6-dichloro-9-phenyl-8-azapurine, stirred with potassium carbonate in methanol (room temp, 20 h), was claimed to give an 83% yield of 2,6-dimethoxy-9-phenyl-8-azapurine.¹²⁸

d. *Conversion to Primary Amines.* 6-Chloro-7-methyl-8-azapurine gave an 80% yield of the 6-amino analog when refluxed (15 min) with aqueous ammonia.³ Ethanolic ammonia was preferred for more lipophilic compounds and was used under reflux⁵⁹ or in a sealed tube.¹¹⁷ 2,6-Dichloro-8-methyl-8-azapurine, in ethanolic ammonia, required 12 h at 170°C for replacement of both chlorine atoms (62% yield).⁵³

2-Amino-6-chloro-9-(2,3-dihydroxy-4-hydroxymethyl)cyclopentyl-8-

¹²⁴ Y. F. Shealy, J. D. Clayton, C. A. O'Dell, and J. A. Montgomery, *J. Org. Chem.* **27**, 4518 (1962).

¹²⁵ Y. F. Shealy, R. F. Struck, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.* **26**, 4433 (1961).

¹²⁶ Y. F. Shealy, J. D. Clayton, and C. A. O'Dell, *J. Heterocycl. Chem.* **10**, 601 (1973).

^{126a} A. Da Settimo, O. Livi, P. L. Ferrarini, and G. Primofiore, *Farmaco, Ed. Sci.* **35**, 298 (1980).

¹²⁷ T. Higashino, T. Katori, and E. Hayashi, *Yakugaku Zasshi* **99**, 1031 (1979).

¹²⁸ S. S. Pharmaceutical Co., Ltd., Japanese Patent (59) 62,595 (1984) [*CA* **101**, 72754 (1984)].

azapurine was converted to the 2,6-diamino analog by heating in liquid ammonia (60°C, 18h).¹²⁹

e. *Other Amines.* 6-Chloro-8-azapurine, refluxed with benzylamine in butanol, gave a 91% yield of the secondary amine; ethylamine in butanol (100°C, 3 h; sealed tube) gave 91% of 6-butylamino-8-azapurine.¹¹⁷ 6-Chloro-9-methyl-¹²⁷ and -9-phenyl-8-azapurine⁷⁹ were converted to the corresponding secondary and tertiary amines, usually at room temperature in benzene (1 h or less), with methylamine, diethylamine, butylamine, aniline, cyclohexylamine, benzylamine, hydrazine, and hydroxylamine (40–95% yields). For other replacements by hydrazine, see refs. 2, 3, 59, and 117. For condensations with amino acids or histamine, see ref. 117.

f. *Conversion to Sulfur-Containing Analogs.* 9-Benzyl-6-chloro-8-azapurine, refluxed with thiourea in methanol (15 min), gave 9-benzyl-8-azapurine-6-thione in 90% yield,⁹⁹ and there are many similar examples.^{3,59,117,118}

2-Amino-6-chloro-9-(2,3-dihydroxy-4-hydroxymethyl)cyclopentyl-8-azapurine was converted to the 6-methylthio analog, by methanethiol in methanolic sodium methoxide (82% yield).¹²⁹

6-Chloro-9-phenyl-8-azapurine, stirred with sodium *p*-toluenesulfonate in dimethylformamide (room temp, 12 min), gave a 41% yield of 9-phenyl-6-*p*-toluenesulfonyl-8-azapurine.¹³⁰ The new substituent was shown to be only moderately useful for metatheses.^{79,127}

g. *Reaction with Carbon Nucleophiles.* 6-Chloro-9-methyl-8-azapurine condensed¹²⁷ with the following reagents in dimethylformamide and sodium hydride (room temp, 1–3 h; 53–76% yields): malononitrile, phenylacetonitrile, ethyl cyanoacetate, ethyl acetoacetate, diethyl malonate, and acetylacetone; whereas acetone, acetophenone, and cyclohexanone reacted only slightly. Thus diethyl malonate gave 6-bis(ethoxycarbonyl)methyl-9-methyl-8-azapurine. 6-Chloro-9-phenyl-8-azapurine reacted similarly, but not so cleanly.⁷⁹

h. *Miscellaneous.* 2-Amino-6-chloro-9-ethyl-8-azapurine and triisopropyl phosphite gave diisopropyl 2-amino-9-ethyl-8-azapurine-6-phosphonate in 64% yield (170°C, 7 h).¹²⁵ 7-Chloro-9-methyl-¹²⁷ and 9-phenyl-8-azapurine⁷⁹ were converted to the 6-cyano analogs by reaction with potassium cyanide in dimethylformamide, with external cooling (yields 40–49%).^{79,127}

¹²⁹ Y. F. Shealy, J. D. Clayton, G. Arnett, and W. M. Shannon, *J. Med. Chem.* **27**, 670 (1984).

¹³⁰ S. S. Pharmaceutical Co., Ltd., Japanese Patent 131, 587 (1981) [*CA* **96**, 122819 (1982)].

6. "Mercapto" (Thioxo), Methylthio, Methylsulfonyl, and Arylsulfonyl Groups

a. *The Thione Function.* Attempts at desulfurization have usually failed; the following may be unique. 8-Benzyl-8-azapurine-6-thione and Raney nickel, refluxed in methanol (2 h), yielded 75% of 8-benzyl-1,6-dihydro-8-azapurine.⁷²

Methylation of 2- and 6-thiones has been found to take place exclusively on the sulfur atom, and many examples are recorded. Usually, the thione was stirred with iodomethane (1.1 equiv) in *N* sodium hydroxide (25°C, 15–60 min), and yields often exceeded 85%.^{2,53,59,72} Thus 9-benzyl-8-azapurine-2,6-dithione gave 9-benzyl-2,6-bis(methylthio)-8-azapurine in 93% yield.⁸⁸ 7-Methyl- and 8-methyl-1,6-dihydro-8-azapurine-2-thione reacted similarly.⁸²

b. *The Methylthio Group.* The methylthio group is versatile. It has been eliminated by reduction, replaced by oxygen, or simply demethylated. It has been replaced by alkoxy or amino groups, also oxidized to sulfinyl and sulfonyl functions. Examples follow.

6-Dimethylamino-9-ethyl-2-methylthio-8-azapurine, heated with Raney nickel in methoxyethanol (100°C, 1 h), gave a 20% yield of 6-dimethylamino-9-ethyl-8-azapurine.¹³¹

7-, 8-, and 9-Methyl-6-methylthio-8-azapurines were rapidly converted to the 6-thiones by cold aqueous ammonium sulfide (no yields given).¹³² 8-Methyl-6-methylthio-8-azapurine and ammonium selenide solution (100°C, 30 min) gave 8-methyl-6-seleno-8-azapurine in 85% yield.¹³²

9-Methyl-6-methylthio-8-azapurine, stirred with potassium permanganate in cold, dilute acetic acid, produced an 80% yield of 9-methyl-8-azapurin-6-one.⁵⁹ Hydrogen peroxide in acetic acid has also been used for this type of reaction (no yield given).¹⁰⁶

9-Methyl-6-methylthio-8-azapurine, refluxed for 2 h with aqueous ammonia, produced a 90% yield of 6-amino-9-methyl-8-azapurine.¹³³ In parallel cases, ethanolic ammonia was used at 130–150°C.^{2,53} 7-Methyl- and 8-methyl-2,6-bis(methylthio)-8-azapurine and ethanolic ammonia (130°C, 12 h) gave 6-amino-7- or -8-methyl-2-methylthio-8-azapurine in 90% yield.⁵¹

6-Methylthio-8-azapurine, heated with butylamine in ethanol (120°C, 5 h), yielded 70% of the 6-butylamino analog; 7-methyl-6-methylthio-8-aza-

¹³¹ R. B. Angier and J. W. Marsico, *J. Org. Chem.* **25**, 759 (1960).

¹³² F. Bergmann, M. Rashi, U. Reichman, and Z. Neiman, *Isr. J. Chem.* **8**, 919 (1970).

¹³³ R. Weiss, R. K. Robins, and C. W. Noell, *J. Org. Chem.* **25**, 765 (1960).

purine and dimethylamine similarly gave the 6-dimethylamino analog (80%).⁷⁵ 6-Methylthio-8-azapurine, refluxed in aqueous dimethylamine (3 h), gave an 80% yield of 6-dimethylamino-8-azapurine.¹³³ 9-Benzyl-6-methylthio-8-azapurine and hydrazine hydrate, mixed in boiling methanol and rapidly cooled, yielded 95% of 9-benzyl-6-hydrazino-8-azapurine, and several analogs were made similarly.^{59,72}

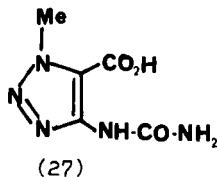
8-Methyl-6-methylthio-8-azapurine, refluxed (1 h) with methanolic sodium methoxide, gave 6-methoxy-8-methyl-8-azapurine in 50% yield.²

3-Chloroperbenzoic acid and 8-methyl-2-methylthio-8-azapurine, stirred in chloroform (20°C, 12 h) yielded 60% of 8-methyl-2-methylsulfonyl-8-azapurine.⁸² The same acid converted 6-amino-2-methylthio-8-azapurine 9-ribose to the 2-methylsulfonyl analog in 80% yield (50°C, 1 h).¹²¹ 6-Amino-7-methyl- and -8-methyl-2-methylthio-8-azapurine and potassium permanganate, stirred in cold, dilute acetic acid, yielded 88% of the sulfone; 8-methyl-2,6-bis(methylthio)-8-azapurine, treated similarly, yielded 64% of 8-methyl-2-methylsulfonyl-8-azapurin-6-one.⁵³

c. The Methylsulfonyl Group. 7-Methyl-2-methylsulfonyl-8-azapurin-6-one and ethanolic ammonia (160°C, 12 h) gave 2-amino-7-methyl-8-azapurin-6-one (90%). 6-Amino-7-methyl-2-methylsulfonyl-8-azapurine similarly yielded 70% of the 2,6-diamine.⁵³ 6-Amino-2-methylsulfonyl-8-azapurine 9-ribose and ethanolic ammonia (5°C, 2 days) gave the 2,6-diamine riboside in 85% yield.¹²¹

6-Amino-7-methyl- and -8-methyl-2-methylsulfonyl-8-azapurine, refluxed (2 h) in methanolic sodium methoxide, gave the 2-methoxy analogs (80% yields). 8-Methyl-2-methylsulfonyl-8-azapurin-6-one, refluxed with ethanolic sodium ethoxide, furnished 89% of the 2-ethoxy analog.⁵³

Hydrolysis of the 2-methylsulfonyl group to a 2-oxo function in similar compounds was effected by stirring for 1 day at room temperature with *N* potassium hydroxide. Exceptionally, 7-methyl-2-methylsulfonyl-8-azapurin-6-one underwent further hydrolysis to 1-methyl-4-ureido-1,2,3-triazole-5-carboxylic acid (27).⁵³



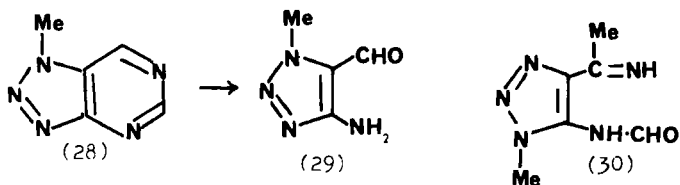
9-Phenyl-6-*p*-toluenesulfonyl-8-azapurine, stirred with ammonia and, severally, with amines in chloroform (room temp, 5–180 min), gave 50–85% yields of the 6-amino derivatives, primary, secondary, and tertiary.⁷⁹ Similar

reactions were carried out with sodium alkoxides (25–80°C) and Michael reagents. It was concluded that 9-phenyl-6-chloro-8-azapurine gave better yields in all of these reactions.⁷⁹

C. RING OPENINGS AND REARRANGEMENTS

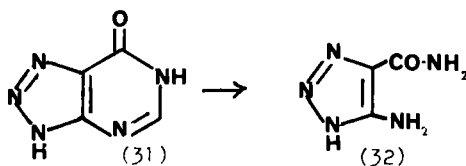
1. Ring Opening without Reclosure

When 7-, 8-, or 9-methyl- or 8- or 9-benzyl-8-azapurines were set aside in aqueous *N* hydrochloric acid (25°C, about 1 day), they were completely hydrolyzed to the 1-, 2-, or 3-methyl, or 8- or 9-benzyl derivatives, respectively, of 4-amino-1,2,3-triazole-5-carbaldehyde, as in **28** → **29**. A methyl group in the 2 position precluded this reaction. 6,9-Dimethyl-8-azapurine gave the analogous ketone, 4-amino-3-methyl-1,2,3-triazol-5-yl methyl ketone.¹³⁴



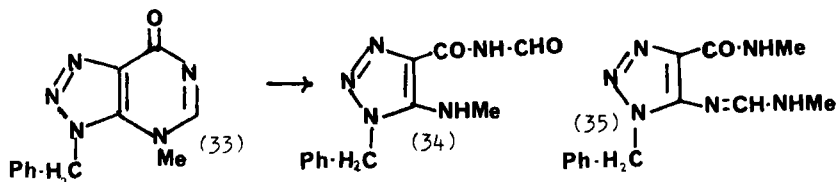
Cold aqueous *N* sodium hydroxide gave similar results, except that a 2-methyl group did not interfere with the hydrolysis. The alkaline ring opening of 6,9-dimethyl-8-azapurine stopped at 4-formamido-3-methyl-1,2,3-triazol-5-yl methyl ketone. This result indicated that the first stage in the reaction is **30**. Similar 4-formamido-5-formytriazoles were isolated at an early stage in several of the other hydrolyses.¹³⁴

A plot of time versus $\log(A_0/A)$, produced a straight line, indicating first-order kinetics. The calculated half-lives for disappearance of the starting material showed that the alkaline hydrolysis was faster. This reaction has preparative utility for 4-formamidotriazole-5-carbaldehydes, which cannot¹¹⁹ be made by direct formylation.¹³⁴

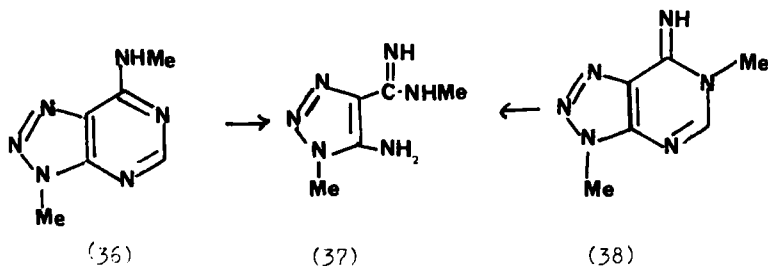


¹³⁴ A. Albert and C. J. Lin, *J. Chem. Soc. C*, 1819 (1977).

The hydrolysis of an 8-azapurinone usually was more difficult. Thus, 8-azapurin-6-one (31) required heating (with 2 *N* hydrochloric acid, 90°C, 2 h) for hydrolysis to 4-amino-1,2,3-triazole-5-carboxamide (32).¹³⁵ Further stabilization of the pyrimidine ring, as in 2-amino-8-azapurin-6-one, shifted the site of fission to the triazole ring, and consequently more severe conditions were required (6 *N* HCl, 150°C, 2 h). The product was 2,4,5-triaminopyrimidin-6-one.¹³⁵



9-Benzyl-3-methyl-8-azapurin-6-one (33) was more easily hydrolyzed. Stirring with *M* acetic acid (24°C, 20 h) yielded 80% of 3-benzyl-4-methylamino-1,2,3-triazole-5-(*N*-formylcarboxamide) (34).⁶ The isomeric 9-benzyl-1-methyl-8-azapurin-6-one was, surprisingly, converted to 3-benzyl-4-methylaminomethylenamino-1,2,3-triazole-5-(*N*-methylcarboxamide) (35), by stirring with sodium in liquid methylamine.⁵



6-Amino-8-azapurine was converted to 4-amino-1,2,3-triazole-5-carboxamidine in 90% yield when refluxed with *N* hydrochloric acid (2 h).^{75,136} Similar results were given when an alkyl or aralkyl group was present in the 7, 8, or 9 position (e.g., 36 → 37).⁷⁵ The highest yields were obtained when the 6-amino group was secondary, because a primary group underwent some deamination, giving the corresponding 8-azapurin-6-one. The reaction apparently began with rupture of the bond between N-1 and C-2, followed by

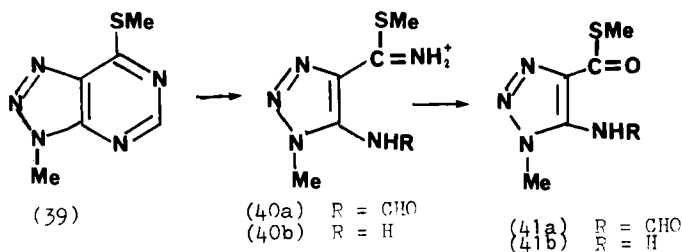
¹³⁵ Y. Hirata, K. Iwashita, and K. Teshima, *Nagoya Sangyo Kagaku, Kenkyusho Kenkyu Hokoku* 9, 83 (1957) [*CA* 51, 12074 (1957)].

¹³⁶ Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.* 30, 2488 (1965).

deformylation.⁷⁵ 1-Alkyl-6-imino-1,6-dihydro-8-azapurines proved to be equally successful starting materials for this reaction ($38 \rightarrow 37$).⁷⁵

6-Methylamino-8-azapurine uniquely followed a more complex path. A simultaneous Dimroth rearrangement to 6-amino-9-methyl-8-azapurine (Section C,2) allowed two isomeric amidinotriazoles to be formed, one from each 8-azapurine.⁷⁵ 6-Amino-8-azapurine, when set aside in cupric chloride solution, produced the following complex: tetrachlorobis-2-[(4-amino-5-carboxamidinium)-1,2,3-triazole]copper²⁺, the structure of which was verified by single-crystal X-ray work.³⁵

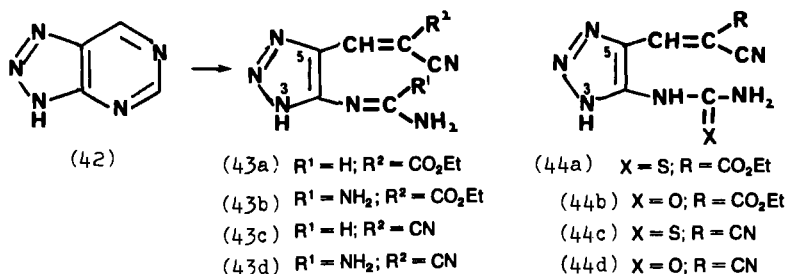
6-Amino-8-azapurine 1-oxide, stirred with 10 *N* hydrochloric acid (room temp, 5 min) gave 4-amino-1,2,3-triazole-6-carboxamidoxime in 81% yield.¹⁰⁴



Although 9-methyl-6-methylthio-8-azapurine (39) was cleanly converted to 9-methyl-8-azapurin-6-one by refluxing for 3 days with *N* acetic acid, the reaction quickly took a different course when a stronger acid was used. When 39 was refluxed with *N* hydrochloric acid for 15 min, 4-amino-3-methyl-5-(methylthio) carbonyl-1,2,3-triazole (41b) was formed in 94% yield. The 7- and 8-methyl isomers, as well as the 9-benzyl analog and 6-methylthio-8-azapurine, all behaved similarly. An intermediate, isolated in 65% yield during hydrolysis at a lower temperature, was identified as 4-amino-3-methyl-1,2,3-triazol-5-yl(methylthio)methyleniminium (cation) (40b). This was unexpected because thioimides are rare in heterocyclic chemistry. The pathway of the reaction was judged to run from the cation of 39, through 40a and 41a, to the end product 41b. This reaction has preparative value because the methylthio group could readily be replaced by secondary amines (at room temp), and the resultant amides were easily cyclized in hot formamide to 1-alkyl-8-azapurin-6-ones.¹³⁷

8-Azapurine (42) and its 2-amino, 2-thioxo, and 2-oxoderivatives, when allowed to react in water with ethyl cyanoacetate (20°C, 0.5–3 h), gave 56–77% yields of 4-aminomethylenamino-4-diaminomethylenamino-, 4-thioureido-, and 4-ureido-5-(2-cyano-2-ethoxycarbonylvinyl)-1,2,3-tria-

¹³⁷ A. Albert, *J. Chem. Soc. C*, 2379 (1969).



zoles (43a, 43b, 44a, and 44b, respectively). Similar reactions with malononitrile (room temp 5–60 min) produced the corresponding derivatives of 5-(2,2-dicyanovinyl)-1,2,3-triazole (43c, 43d, 44c, and 44d, respectively) in 66–96 % yields. The reaction retrogressed to the starting materials when the products were set aside in 0.5 *N* sodium hydroxide (20°C, 5 min) or subjected to sublimation.⁶⁸

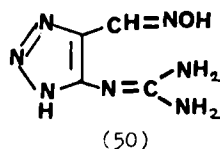
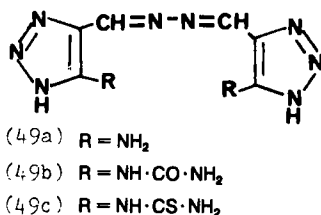
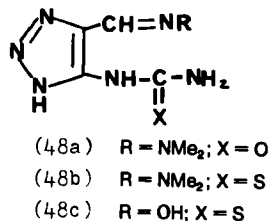
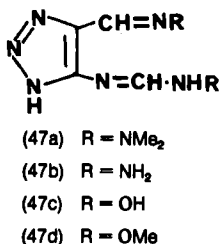
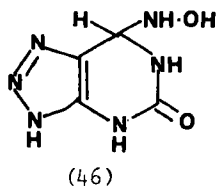
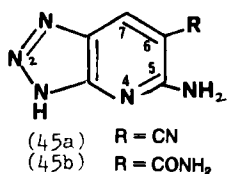
Cyclization to 5-amino-6-cyano-1,2,3-triazolo[4,5-*b*]pyridine (45a) occurred when 43c was heated in 4 *N* sodium hydroxide (90°C, 1 min), through loss of hydrogen cyanide.⁶⁸ Similar ring closures were given by corresponding derivatives of pyrimidine, quinazoline, and purine.¹³⁸ This reaction mechanism was outlined. The nucleophile had to be one that was sufficiently basic to induce, after normal 1,6-addition, the methylene proton to ionize, thus initiating ring opening to give amidines of types 43 and 44. Cyclization to 45 occurred through an attack on the CN triple bond by the nitrogen atom attached to C-4 of the triazole ring; this attack was accompanied by degradation of the amidine chain, leading to loss of HCN. The same product (45a) was formed in 65% yield through loss of HSCN when the potassium salt of 44c was heated (90°C, 5 min), and it was also formed by alkaline treatment of 43d and 43b.⁶⁸

A similar triazolopyridine (45b) was obtained when either 8-azapurine or 8-azapurin-2-one was heated with cyanoacetamide in aqueous potassium hydrogen carbonate (90°C, 3 h).⁶⁸

Most of the other carbon nucleophiles mentioned in Section III,A,2 did not proceed beyond normal 1,6-addition, for example, acetylacetone and ethyl acetoacetate with 8-azapurin-2-one. However, these two reagents behaved exceptionally with the parent (8-azapurine) to yield about 40% of 6-acetyl- and 6-ethoxycarbonyl-5-methyl-1,2,3-triazolo[4,5-*b*]pyridine, respectively, in dilute sulfuric acid (20°C, 16 h).⁶⁸ 9-Methyl- and 9-phenyl-8-azapurine behaved similarly,¹³⁹ and these authors suggested a slightly different mechanism.

¹³⁸ A. Albert and W. Pendergast, *J. C. S. Perkin I*, 1794 (1973).

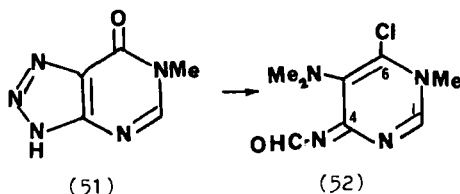
¹³⁹ T. Higashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.* 27, 2861 (1979).



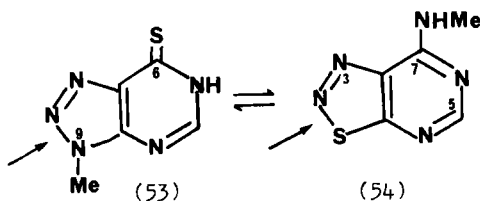
8-Azapurin-2-one gave 62 and 85% yields of simple adducts, such as **46**, with methoxyamine (NH_2OMe) and hydroxylamine, respectively, at pH 4 (room temp 18 h). However, 8-azapurine and its 2-amino and 2-thioxo derivatives underwent further reaction and produced 4-hydroxyaminomethylenamino- (**47c**), 4-diaminomethylenamino- (**50**), and 4-thioureido-1,2,3-triazole-5-carbaldehyde oxime (**48c**) (in 77, 80, and 55% yields, respectively). Similarly, 8-azapurine and methoxyamine gave **47d**.⁷⁴

8-Azapurine and 1,1-dimethylhydrazine, in water, (room temp, 18 h) furnished 4-dimethylhydrazonomethylenamino-1,2,3-triazole-5-carbaldehyde dimethylhydrazone (**47a**). 8-Azapurin-2-one and -2-thione similarly gave the 4-ureido (**48a**) and 4-thioureido (**48b**) analogs (yields, 63 and 77%, respectively). 2-Amino-8-azapurine did not react with this reagent, but with hydrazine it produced a 90% yield of 4-hydrazonomethylenamino-1,2,3-triazole-5-carbaldehyde hydrazone (**47b**). On the other hand, 8-azapurine and its 2-oxo and 2-thioxo derivatives underwent a 2:1 reaction with hydrazine (under the same conditions) to give the azines **49a**, **b**, **c**, respectively, in 72–88% yields.⁷⁴

8-Azapurine and its 2-substituted derivatives were insufficiently nucleophilic to react with ammonia or with primary amines under these conditions.⁷⁴



When 1-methyl-8-azapurin-6-one (51) was refluxed with thionyl chloride and dimethylformamide in chloroform (4 h), 6-chloro-4-formylimino-1-methyl-5-dimethylamino-1,6-dihydropyrimidine (52) was formed in 41% yield.



2. Ring Opening with Spontaneous Reclosure

7- and 8-Methyl-8-azapurin-6-ones reacted normally with phosphorus pentasulfide in boiling pyridine to give the corresponding 6-thiones, but rearrangement took place when this reaction was attempted with 8-azapurin-6-one or its 9-methyl derivative. Here, the expected 6-thione, e.g., 53, isomerized to 7-methylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (54).^{59,140} The latter was found to be convertible to 53 by refluxing with *N* sodium hydroxide for 5 min, chilling, and acidifying. Ring opening, where marked by an arrow in 53 and 54, allows interconversion via a diazonium thioanhydride. The susceptible 8-azapurine-6-thiones could be converted to the isomeric (alkali-insoluble) thiadiazolopyrimidines by refluxing in ethanol, or simply by storing under warm conditions. In historical fact, this reaction was discovered during the usual December heat wave in Australia¹⁴⁰ and came to be called the Christmas rearrangement.⁸⁸

Earlier authors who claimed to have prepared 8-azapurine-6-thione by the phosphorus pentasulfide reaction had isolated only the thiadiazolopyrimidine, as the UV spectrum clearly shows.¹⁴¹

8-Azapurine-2,6-thione, refluxed for 1 h in butanol, quantitatively depos-

¹⁴⁰ A. Albert and K. Tratt, *Angew. Chem., Int. Ed. Engl.* **5**, 587 (1966).

¹⁴¹ C. T. Bahner, B. Stump, and M. E. Brown, *J. Am. Chem. Soc.* **75**, 6301 (1953).

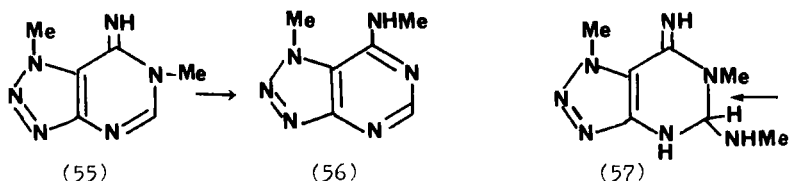
ited the isomeric 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-5-thione, a reaction quickly reversed by boiling with *N* sodium hydroxide.⁸⁸ This shows that retrogression of the Christmas rearrangement is not driven solely by ability to escape, as anion, from the tautomeric equilibrium, because both isomers are, in this case, acids. A similar phosphorus pentasulfide reaction converted 1,3-dimethyl-8-azapurine-2,6-dione to 7-imino-4,6-dimethylthiadiazolo[5,4-*d*]pyrimidine-5-thione, whose imino group was rapidly hydrolyzed (to an oxo group) by boiling with water.¹⁴²

The kinetics for the Christmas rearrangement of 9-benzyl- and of variously 4-substituted 9-phenyl-8-azapurine-6-thiones were found to be first order, and the rate constants and equilibrium constants were recorded. A plot of log forward component versus Hammett's sigma values for the 4-phenyl substituents was rectilinear. The 8-azapurine isomer was disfavored by electron-withdrawing substituents and by increased temperatures. In dimethyl sulfoxide, the equilibrium favored the 8-azapurine isomer more than in alcohols. Ultraviolet monitoring of the reaction, in both directions, detected no buildup of any acyclic intermediate.¹¹⁸

No oxadiazolotriazole could be detected when 9-benzyl-8-azapurin-6-one was heated at 200°C.⁵⁹

The term "Dimroth rearrangement" was coined¹⁴³ in 1963 to characterize a large family of isomerizations of which some of the earliest examples had been studied by Otto Dimroth in 1909.¹⁴⁴ In this type of ring opening followed by closure, a ring-nitrogen atom, one that bears an alkyl group, exchanges place with an exocyclic imino group, to which it is linked by a carbon atom, in an amidine-like structure. The subject has been well reviewed.¹⁴⁵

In the 8-azapurine series, methylamine acetate (but not the traditionally used free amine) quantitatively changed 6-imino-1,7-dimethyl-1,6-dihydro-8-azapurine (**55**) to 7-methyl-6-methylamino-8-azapurine (**56**) (65°C, 2 h). The 1,8- and 1,9-dimethyl isomers and also the 9-benzyl-1-methyl analog



¹⁴² S. Nishigaki, K. Shimizu, and K. Senga, *Chem. Pharm. Bull.* **25**, 2790 (1977).

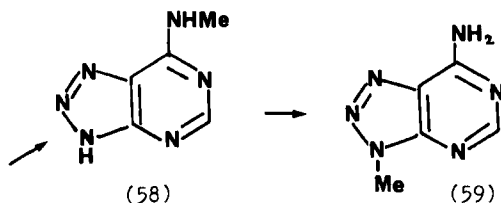
¹⁴³ D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963).

¹⁴⁴ O. Dimroth, *Justus Liebigs Ann. Chem.* **364**, 183 (1909).

¹⁴⁵ D. J. Brown, in "Mechanisms of Molecular Migrations" (B. S. Thyagarajan, ed.), Vol. 1, p. 209. Wiley (Interscience), New York, 1968.

behaved similarly. The agent (methylamine, sparingly but steadily available from the acetate at the pervading pH of 6.2) added across the most delocalized C=N bond, thus providing C-2 with three electron-withdrawing groups, as in 57, and leading to ring fission at the arrow point.⁸⁷

In another type of Dimroth rearrangement, the triazole, rather than the pyrimidine ring, underwent the change. 6-Methylamino-8-azapurine (58), refluxed in dimethylformamide (14 h), assumed an equilibrium in which 9-methyl-6-amino-8-azapurine (59) predominated in a 3:1 ratio; it was separated through its insolubility in alkali. This reaction was recommended as the best synthesis of 59, as it avoids the detonating reagent methyl azide.⁷⁵ Similarly, 2-amino-6-ethylamino-8-azapurine gave 2,6-diamino-9-ethyl-8-azapurine quantitatively, although its potassium salt did not undergo this reaction.¹⁴⁶



For other examples of the Dimroth rearrangement and its retrogression, see Section IV,B,1.

It has not yet been established how the apparent migration of *N*-methyl groups (as described in Section III,A,1) from the 7 or 8 to the 9 positions of 8-azapurines takes place.

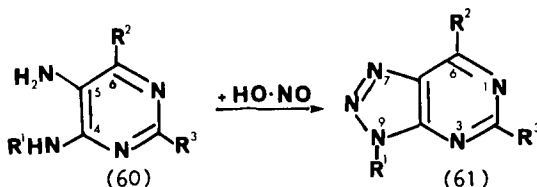
IV. Synthesis

Commencing an 8-azapurine synthesis offers the chemist a choice between starting with a pyrimidine or a 1,2,3-triazole. Help in selecting the best route is offered in Section IV,C.

A. ANNELENATION OF A TRIAZOLE RING ON TO AN EXISTING PYRIMIDINE RING

The original Traube synthesis, conveniently generalized as 60 \rightarrow 61, has proved suitable for preparing many 8-azapurines. The R¹ group may be

¹⁴⁶ C. Temple, B. H. Smith, and J. A. Montgomery, *J. C. S. Chem. Commun.*, 52 (1972).



hydrogen, or an alkyl, aralkyl, or aryl group. Required for antiviral and anticancer work, many examples have R^1 as cyclopentyl (with or without hydroxy substituents).^{126,129,147-149} Also, R^1 may be a sugar residue. In an example of 9-glycosylation, the amino group of 2,3-*O*-isopropylidene-D-ribofuranosylamine was condensed with the chlorine atom of 2-acetamido-4-benzylthio-6-chloro-5-nitropyrimidine. The nitro group in the product was reduced, and the resulting 4,5-diaminopyrimidine was cyclized with nitrous acid.¹⁰⁶ However, most syntheses of 9-ribosyl-8-azapurines are effected by glycosylation of a preformed 8-azapurine (Section III,A,1) or of a 1,2,3-triazole, which is later transformed into an 8-azapurine (Section IV,B).

The Traube synthesis has proved to be compatible with many kinds of groups in the starting pyrimidine (R^2 and R^3 in **60**), even with the thioxo (mercapto) and primary amino groups. Pyrimidine *N*-oxides are also acceptable.^{123a} Moreover, 8-azapurines with substituents in the usually difficult 1 and 3 positions have been formed by Traube reactions (refs. 150 and 151, respectively). 2-Pyrimidyl-8-azapurines have also been produced in this way.¹⁵² The Traube reaction permitted amino-acid substituents (as R^1 in **60**) to retain full optical purity.¹⁵³ Radioactive labeling survived well when a diaminopyrimidine, made in five steps from diethyl malonate-*l*-¹⁴C, was cyclized.¹⁴⁹

When R^2 (in **60**) was a chlorine atom, the conditions were slightly modified to prevent its hydrolysis.^{117,118,124} The conversion of a methyl group (in R^2) to an aldoxime (see Section III,B,1) was found avoidable by a modification^{48,154} as was the hydrolysis of a 2-primary amino group (R^3) to an 8-azapurin-2-one.¹⁵⁵

¹⁴⁷ Y. F. Shealy, C. A. O'Dell, W. M. Shannon, and G. Arnett, *J. Med. Chem.* **27**, 1416 (1984).

¹⁴⁸ Y. F. Shealy and J. D. Clayton, *J. Pharm. Sci.* **62**, 1432 (1973).

¹⁴⁹ P. K. Chang, L. J. Sciarini, A. C. Sartorelli, and M. S. Zedek, *J. Med. Chem.* **11**, 513 (1968).

¹⁵⁰ J. J. Fox and D. van Praag, *J. Am. Chem. Soc.* **26**, 526 (1961).

¹⁵¹ T. Kishikawa and H. Yuki, *Chem. Pharm. Bull.* **14**, 1365 (1966); M. Ridi, G. Franchi, S. Mangiavacchi, and M. P. Lombardini, *Boll. Chim. Farm.* **107**, 401 (1968) [*CA* **69**, 96637 (1968)].

¹⁵² D. J. Brown, S.-B. Lan, and K. Mori, *Aust. J. Chem.* **37**, 2093 (1984).

¹⁵³ E. Kraas, E. Stark, F. Tjoeng, and E. Breitmaier, *Chem. Ber.* **108**, 1111 (1975).

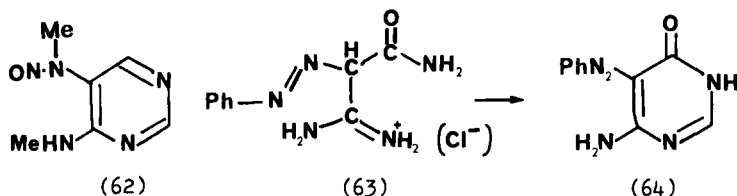
¹⁵⁴ P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta* **34**, 835 (1951).

¹⁵⁵ F. Bergmann, G. Levin, and H. Kwietny, *Arch. Biochem.* **80**, 318 (1959).

For performing a Traube synthesis, two methods have been found best. In the first, the selected pyrimidine (**60**) was dissolved in water as its hydrochloride (or in dilute hydrochloric or acetic acid) and stirred with sodium nitrite at 0°C, after which it was often (but not necessarily) heated at 60–100°C.^{4,118} In the second method, the pyrimidine (**60**), as free base, was refluxed for 2–10 min with a mixture of isopentyl nitrite and a solvent such as ethanol^{48,154} or dioxane¹²⁴ (the nitrite alone is a poor solvent). This second method has been most used for examples where R² and R³ (in **60**) are not hydrogen-bonding substituents.

A special case arises where R² (in **60**) is a primary amino group and R¹ is an alkyl or glycosyl group. Here, cyclization always favors the secondary amine, so that R¹ appears exclusively on the 9 position of the product.^{133,156,157}

A daring expedient to obtain the right starting material was the alkaline cleavage of a similarly substituted *purine* (0.5 *N* NaOH, room temp, 1 h) to give 6-chloro-5-formamido-4[(2,3-*O*-isopropylidene-*D*-ribofuranosyl)-amino]pyrimidine, from which the formyl group was removed by acid hydrolysis, followed by formation of the triazole ring with aqueous nitrous acid (optical purity was retained).¹⁵⁸



A notable deficiency of the Traube synthesis is its inability to produce 7- or 8-substituted 8-azapurines. All attempts to make 7-methyl-8-azapurine from 4-amino-5-methylaminopyrimidine and nitrous acid produced only the *N*-5-nitroso derivative **62**, which remained unchanged by refluxing with ethanolic sodium ethoxide and was acetylated only at N-4 by heating with acetic anhydride.⁴⁸ Likewise, 4-amino-5-benzylaminopyrimidine-2,6-dione produced the 5-benzylnitrosoamino analog, which resisted cyclization.⁶⁰

Phenylazomalonamideamidinium hydrochloride (**63**), when heated with formamide at 170°C, was converted to 4-amino-5-phenylazopyrimidin-6-one (**64**) (63% yield), which was oxidized to 8-phenyl-8-azapurin-6-one by cupric sulfate in aqueous pyridine (100°C, 24 h, 18% yield).¹⁵⁹ (For a more economical use of **63**, see Section IV.B). Similarly, heating phenylazoma-

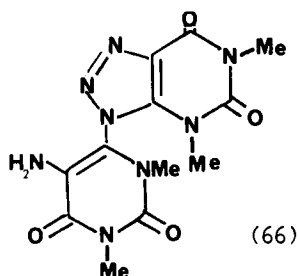
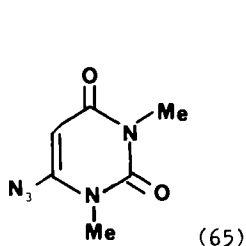
¹⁵⁶ J. Davoll, *J. Chem. Soc.*, 1593 (1958).

¹⁵⁷ J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.*, 1651, 3606 (1958).

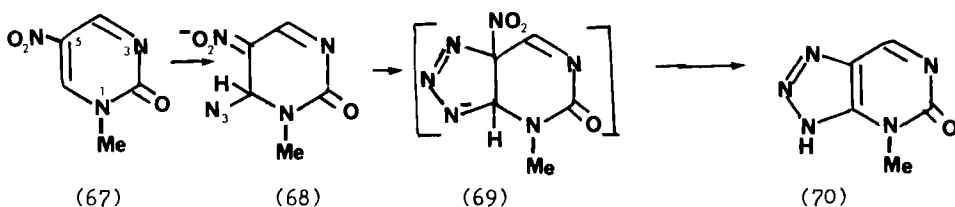
¹⁵⁸ J. A. Montgomery and H. J. Thomas, *J. Org. Chem.* **36**, 1962 (1971).

¹⁵⁹ E. Richter and E. C. Taylor, *J. Am. Chem. Soc.* **78**, 5848 (1956).

lonodiamidine dihydrochloride with formamide gave 4,6-diamino-5-phenylazopyrimidine (71% yield), which was oxidized to 6-amino-8-phenyl-8-azapurine in 49% yield.¹⁵⁹ These procedures have developed from the Benson synthesis of 1950, in which 2,4-diaminopyrimidin-6-one was coupled with benzenediazonium chloride and the resulting 5-phenylazopyrimidine was oxidized (as above) to 2-amino-8-phenyl-8-azapurin-6-one.¹⁶⁰ The defect of all these syntheses is that they can produce only 8-azapurines bearing an aryl group in the 8 position. Later, lead tetracetate has been introduced for these oxidations.¹⁶¹



Now follow several later synthetic methods, some of them of limited general application. 6-Azido-1,3-dimethylpyrimidine-2,4-dione (**65**), when refluxed with potassium carbonate in dimethylformamide, yielded 30% of 1,3-dimethyl-8-azapurine-2,6-dione. Inclusion of an alkyl halide in the reaction mixture gave an N-alkylated product (77% yield for methyl iodide, much less for other halides). The alkyl group was assigned to the 7 position without proof.¹⁶² Omission of the potassium carbonate gave the more complex molecule **66**.¹⁶³



1-Methyl-5-nitropyrimidin-2-one (**67**) and sodium azide in dimethylformamide produced 3-methyl-8-azapurin-2-one (**70**). Good evidence was

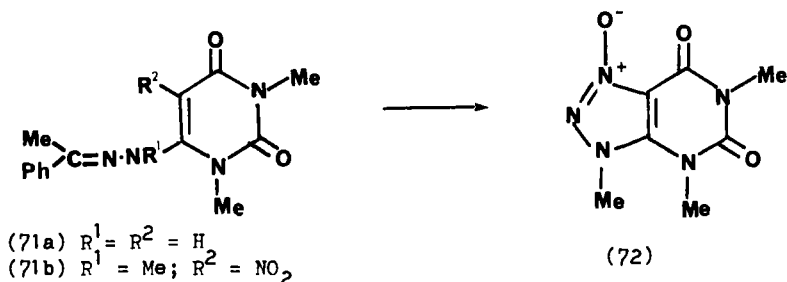
¹⁶⁰ F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Am. Chem. Soc.* **72**, 1816 (1950); L. W. Hartzel and F. R. Benson, *ibid.* **76**, 2263 (1954).

¹⁶¹ Y. Maki and E. C. Taylor, *Chem. Pharm. Bull.* **20**, 605 (1972).

¹⁶² K. Senga, M. Ichiba, and S. Nishigaki, *Heterocycles* **6**, 1915 (1977).

¹⁶³ K. Hirota, K. Maruhashi, T. Asao, and S. Senoa, *Chem. Pharm. Bull.* **30**, 3377 (1982).

adduced for **68** as the first intermediate, and **69** was favored for the penultimate stage. The reaction worked well also when an amino or an oxo substituent was present in the 4 position, or when a glycosyl group replaced methyl in the 1 position. The reaction did not go well when the 1 position was unoccupied, unless both 2 and 4 positions were filled with electron-yielding substituents (principally NH_2 and O). Yields ranged from 50 to 94%, and optimal conditions were 90°C for 3–144 h.¹⁶⁴



1,3-Dimethyl-6-(α -methylbenzylidenehydrazino)pyrimidine-2,4-dione (**71a**) (made from 1,3-dimethyl-6-hydrazinouracil and acetophenone), when refluxed with *N*-nitrosodimethylaniline and phosphoryl chloride in benzene (30 min), gave a 72% yield of 1,3-dimethyl-8-(1-phenylvinyl)-8-azapurine-2,6-dione (**24**), whose convertibility to 1,3-dimethyl-8-azapurine-2,6-dione is described in Section III,B,1.¹¹⁶

Photolysis (10 h) of 1,3-dimethyl-5-nitro-6-(1-methyl-2-acetophenylidenehydrazino)pyrimidine-2,4-dione (**71b**) in acetonitrile gave an "excellent yield" of 2,6-dioxo-1,3,9-trimethyl-8-azapurine 7-*N*-oxide (**72**). This product was apparently formed by the addition of a photoexcited NO_2 group across the exocyclic double bond, followed by rearrangement of the tricyclic (dioxatriaza) product.¹⁶⁵

B. ANNELEMENT OF A PYRIMIDINE RING ON TO AN EXISTING TRIAZOLE RING

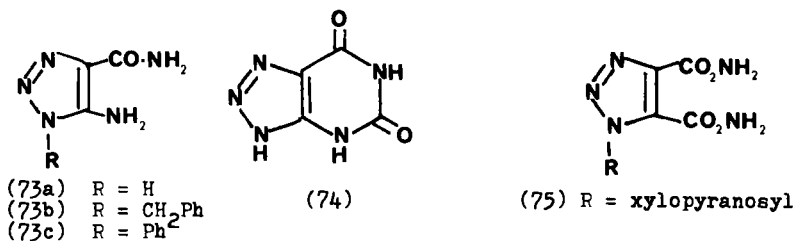
For more than half a century, every preparation of an 8-azapurine began from a pyrimidine intermediate. The possibilities of 1,2,3-triazoles as starting materials were first realized in a burst of publications in 1956–1960.^{157,159,166,167} In large measure, this new activity sprang from Hoover and

¹⁶⁴ H. U. Blank, I. Wempfen, and J. J. Fox, *J. Org. Chem.* **35**, 1131 (1970).

¹⁶⁵ Y. Maki, M. Suzuki, K. Izuta, and S. Iwai, *Chem. Pharm. Bull.* **22**, 1269 (1974).

¹⁶⁶ S. Yamada, T. Mizoguchi, and A. Ayata, *Yakugaku Zasshi* **77**, 455 (1957).

¹⁶⁷ A. Dornow and J. Helberg, *Chem. Ber.* **93**, 2001 (1960).



Day's recent publication of a facile synthesis of 4-amino-1,2,3-triazole-5-carboxamide (73a) and its 3-benzyl derivative (from cyanoacetamide and benzyl azide),¹⁶⁸

1. From Rings with an Amino Group Adjacent to an Acid Amide, Thioamide, or Ester Group

The synthesis from triazoles that, in spite of the poor yield (19%), most shaped future practice was that of Yamada¹⁶⁶ who, by heating 4-amino-1,2,3-triazole-5-carboxamide (73a) with urea (165°C, 5 h), obtained 8-azapurine-2,6-dione (74) plus the intermediate 4-ureido-1,2,3-triazole-5-carboxamide.

Dornow and Helberg¹⁶⁷ expanded this approach by "boiling" 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide (73b) with formamide (80 min), which yielded 77% of 9-benzyl-8-azapurin-6-one. The phenyl analog (73c) similarly gave 9-phenyl-8-azapurin-6-one, in 78% yield, which fell to 31% when a mixture of triethyl orthoformate and acetic anhydride replaced the formamide. An equally successful starting material was 4-anilino-1,2,3-triazole-5-carboxamide, which apparently underwent a Dimroth rearrangement (Section III,C,2) before cyclizing in the formamide. However, the ethyl ester corresponding to 73c produced, in formamide, only a 66% yield of 9-phenyl-8-azapurin-6-one. This result, combined with the poor yield obtained in preparing the ester, as compared to the amide,¹⁶⁸ led to preference for the latter in later work.

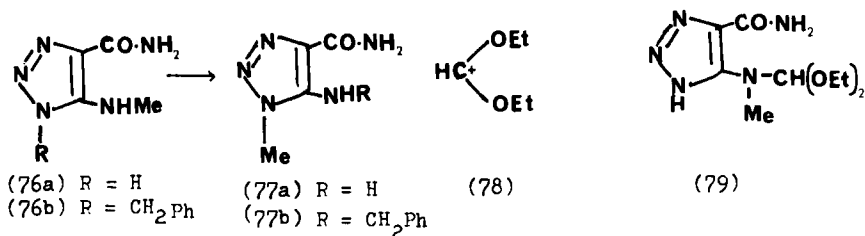
Two related syntheses of this period must be noted. The malonamide derivative 63, when heated with ammoniacal cupric sulfate (100°C, 3 h), yielded 95% of 4-amino-2-phenyl-1,2,3-triazole-5-carboxamide, which was converted to 8-phenyl-8-azapurin-6-one in 67% yield by refluxing with triethyl orthoformate and acetic anhydride (4 h). Alternatively, the triazole amide was changed to the thioamide with phosphorus pentasulfide (79% conversion). This thioamide produced 8-phenyl-8-azapurine-6-thione when

¹⁶⁸ J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.* **78**, 5832 (1956).

cyclized in the same way (64% yield).¹⁵⁹ The limitation of this synthesis is that it can furnish only 8-azapurines with an 8-phenyl substituent. In the other synthesis, 3-xylopyranosyl-1,2,3-triazole-4,5-dicarboxamide (75), subjected to a Hofmann reaction with sodium hypobromite (2°C, 18 h), directly furnished a mixture of 7- and 9-xylopyranosyl-8-azapurine-2,6-dione.¹⁵⁷ The dichotomous course of this reaction discouraged further uses.

Yields from the formamide condensations of 4-aminotriazole-5-carboxamides were improved by use of fixed-temperature baths maintained (usually) at 220°C,^{2,53,59,137} rather than by relying on the "boiling point" of formamide, variously given as 195 and 210°C, but actually masked by the copious escape of ammonia and carbon monoxide. Thanks to this precaution, the yield of 9-benzyl-8-azapurin-6-one, for example, was raised from 77¹⁶⁷ to 95%⁵⁹

The preferred time for formamide condensations became fixed at about 45 min. The presence of a formyl substituent on the 4-amino group was found to improve the yield.² When the 5-amide group was alkylated, yields of 85–95% were obtained.^{5,137} However, when the 4-amino group was alkylated, Dimroth retrogression took precedence over ring closure. For example, 4-methylamino-1,2,3-triazole-5-carboxamide (76a) was converted to 4-amino-3-methyl-1,2,3-triazole-5-carboxamide (77a). As for the corresponding 3-benzyl derivative (76b), the benzyl and methyl groups changed places, giving 77b.⁶ In both reactions the 2,3 bond was broken but reclosed after rotation of the amidine group (see Section III,C,2).



3-Methyl-8-azapurin-6-one was finally obtained from 76a by a most unusual combination of reagents, namely, triethyl orthoformate and 10 *N* hydrochloric acid, with which it was refluxed for 1 h (yield, 86%); 76b similarly gave the 9-benzyl derivative (80% yield).⁶ The stability of the orthoester in 10 *N* acid¹⁶⁹ was attributed to formation of the diethoxycarbene ion (78),¹⁷⁰ which apparently synthesized the acetal 79 from 76a; the desired product was formed from this by loss of two molecules of ethanol.

¹⁶⁹ C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Med. Chem.* **5**, 866 (1962).

¹⁷⁰ M. Ahmad, R. G. Bergstrom, M. J. Cashen, A. J. Kresge, R. A. McClelland, and M. F. Powell, *J. Am. Chem. Soc.* **99**, 4827 (1977).

In 1968, the scope of the formamide condensation was greatly expanded by discovery of practical syntheses for the 1- and 2-methyl derivatives of 4-amino-1,2,3-triazole-5-carboxamide.^{2,3} These, for the first time, made possible the direct preparation, and in excellent yields, of 7- and 8-alkyl-substituted 8-azapurines.^{2,3} These new triazoles also underwent condensation with (an excess of) urea and thiourea (175°C, 1 h, no solvent) to give the correspondingly methylated derivatives of 8-azapurine-2,6-dione (64–89% yield) and 2-thioxo-8-azapurin-6-one (55% yield), respectively.⁵³

Although 4-formamido-1,2,3-triazole-5-carboxamides were deformylated by bases, even 2 *N* sodium carbonate,² an 80% yield of 2-methyl-9-phenyl-8-azapurin-6-one was obtained when 4-acetamido-(also 4-diacetamido)-3-phenyl-1,2,3-triazole-5-carboxamide was refluxed (30 min) with 2.5 *N* sodium hydroxide. Related propionamido and phenylacetamido triazoles gave the corresponding 2-ethyl- and 2-benzyl-8-azapurin-6-ones quantitatively.¹⁷¹ This use of alkali for cyclization was independently discovered and used for making 9-benzyl-2-alkyl-(also 2-aryl)-8-azapurin-6-ones.^{172,173} These alkali-effected closures became sluggish when no *N*-alkyl group was present in the triazole ring due to bonding between 3-H and the acyl oxygen atom,¹⁷² but this pattern of substitution offered no barrier to cyclization of 4-formamidotriazole-5-carboxamides by the formamide method.⁵⁹

The triazole approach is becoming established as a useful route to glycosides of 8-azapurines. 8-Azainosine (9-ribofuranosyl-8-azapurin-6-one) was made (in fewer steps and greater yield than in ref. 70) by condensing cyanoacetamide with 2,3-*O*-isopropylidene-5-*O*-*tert*-butyldiphenylsilyl- β -D-ribofuranosyl 1-azide (in chilled dimethylformamide). The resultant 4-amino-3-(protected)ribofuranosyl-1,2,3-triazole-5-carboxamide (70% yield), after heating with diethoxymethyl acetate [(EtO)₂CHOC(O)Me] (100°C, 3 h), produced a 95% yield of (still protected) 9-ribofuranosyl-8-azapurin-6-one, which, after deprotection, furnished 8-azainosine in 86% yield. Mannopyranoside analogs were made similarly.¹⁷⁴

Radioactive labeling of C-2 was effected by treating 4-amino-1,2,3-triazole-5-carboxamide with acetic formic anhydride (made from H¹⁴CO₂H) and condensing the product with 2,3,5-tri-*O*-benzoyl- α -D-arabofuranosyl bromide. A final methanolysis gave a 53% yield of 9- α -D-arabinofuranosyl-8-azaadenine-2-¹⁴C, with specific activity of 1.83 mCi/mmol.¹⁷⁵ A similar

¹⁷¹ D. R. Sutherland and G. Tennant, *J. Chem. Soc. C* 706 (1971).

¹⁷² Dr. E. Lunt (Dagenham, England), personal communications.

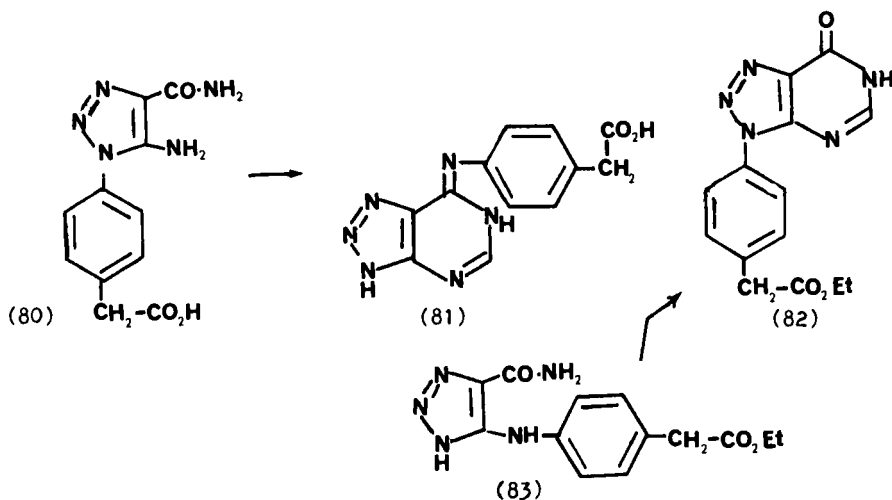
¹⁷³ German Patent 2,162,096 (1972) [CA 77, 101677 (1972)]; British Patent 1,338,235 (1974); U.S. Patent 3,819,631 (1973), to B. J. Broughton, B. J. Large, S. M. Marshall, D. L. Pain, and K. R. H. Wooldridge (May & Baker, Ltd.).

¹⁷⁴ F. Chr  tien and B. Gross, *Tetrahedron* **38**, 103 (1982).

¹⁷⁵ J. A. Montgomery and J. H. Thomas, *J. Labelled Compd. Radiopharm.* **15**, 727 (1978).

synthesis, using tribenzoyl- β -D-arabinofuranosyl azide, produced largely the α product because of anomerization to which the arabinofuranosyl group is prone.¹⁷⁶

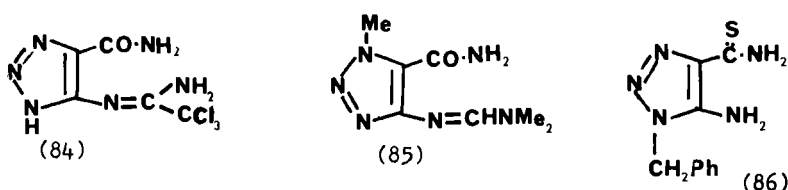
A curious Dimroth rearrangement was noted for those 3-aryl-4-amino-1,2,3-triazole-5-carboxamides whose benzene ring carries an acid group. Thus **80**, heated in formamide (200°C, 1 h) gave a 91% yield of **81**. However, the ethyl ester of **80** behaved normally, producing **82** (64% yield). Curiously, **83**, which is the Dimroth isomer of the ethyl ester of **80**, gave a 60% yield of the 9-aryl-8-azapurinone **82**.^{126a} It was not determined whether these rearrangements occurred at the triazole or the azapurine stage. For more on the Dimroth rearrangement, see Section III,C,2.



The acetates of acetamidine and benzamidine were condensed with 4-aminotriazole-5-carboxamide (**73a**) and its 7- and 8-methyl derivatives to give 2-methyl- and 2-phenyl-8-azapurin-6-ones, respectively, in 80–90% yield, after refluxing for 4–8 h in butanol, hexanol, or octanol (the choice of solvent determined the optimal yield in each case). The reaction with trichloroacetamidine terminated at, e.g., (α -amino- β - β -trichloroethyliden-amino)1,2,3-triazole (**84**) (from **73a**). These intermediates were cyclized to 2-trichloromethyl-8-azapurin-6-ones, in excellent yields, by stirring with 0.5 *N* potassium hydroxide (24°C, 5 h).⁵⁵ This reaction gave only poor yields with **73b,c**.

In a somewhat related reaction, 4-dimethylaminomethylenamino-1-methyl-1,2,3-triazole-5-carboxamide (**85**), and its 2-methyl isomer, when

¹⁷⁶ R. L. Tolman, C. W. Smith, and R. K. Robins, *J. Am. Chem. Soc.* **94**, 2530 (1972).



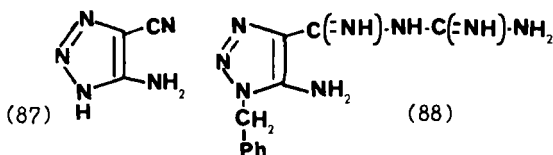
heated in a bath held 15°C above the mp (10 min), gave 7- and 8-methyl-8-azapurin-6-one, respectively, and quantitatively.⁵⁴

4-Amino-3-benzyl-1,2,3-triazole-5-thiocarboxamide (86), when refluxed with triethyl orthoformate and acetic anhydride, yielded 33% of 9-benzyl-8-azapurine-6-thione.⁸⁸

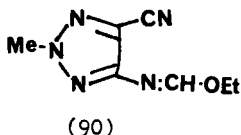
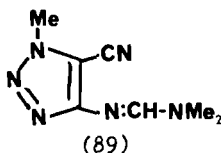
Some sulfur-containing reagents have proved useful for cyclizing 4-amino-1,2,3-triazole-5-carboxamides, variously alkylated in the triazole ring and often on the carboxamide nitrogen atom as well. Trithioorthoesters $[\text{RC}(\text{SEt})_3]$ convert these to the related (2*R*)-8-azapurin-6-ones. Catalysis by boron trifluoride etherate or *p*-toluenesulfonic acid is required, and a suitable solvent is boiling toluene or xylene.¹⁷² *S*-Phenyl thiochloroformate $[\text{PhSC}(\text{O})\text{Cl}]$, in boiling pyridine, cyclized the above triazole carboxamides to the corresponding 8-azapurine-2,6-diones.¹⁷² Methyl isothiocyanate converted 1-methyl-4-amino-1,2,3-triazole-5-carboxamide to 7-methyl-2-thioxo-8-azapurin-6-one.¹⁷²

2. From Rings with an Amino Group Adjacent to a Nitrile, Amidine, or Aldehyde Group

a. *Syntheses from 5-Cyanotriazoles.* 4-Amino-1,2,3-triazole-5-carbonitrile (87) and its 1-, 2-, and 3-methyl, and 3-benzyl derivatives all reacted with the acetates of formamidine, acetamidine, 2,2,2-trichloroacetamidine, and *N,N'*-dibutylformamidine to give the corresponding 6-amino-, 6-amino-2-methyl-, 6-amino-2-trichloromethyl-, and 6-butylamino-8-azapurines, respectively. The reactions were effected in boiling butanol, hexanol, or octanol to suit the chosen amidine and lasted for 0.5–4 h. Yields were 65–90% for formamidine and acetamidine, somewhat less for the others.⁷⁶ 4-Methylaminotriazole-5-carbonitrile and formamidine acetate similarly yielded 89% of 6-amino-3-methyl-8-azapurine.⁶



These nitriles did not condense with guanidine acetate; but, with free guanidine, 4-amino-2-methyl- and -3-benzyl-1,2,3-triazole-5-carbonitrile produced 1-(4-amino-2-methyl- or -3-benzyl-1,2,3-triazol-5-yl)carbonimido-yl)guanidine, e.g., **88**, in 85 and 18% yields respectively. When refluxed in butanol (1 h), **88** was converted to 2,6-diamino-9-benzyl-8-azapurine in 91% yield.⁷⁶



4-Dimethylaminomethylenamino-1-methyl-5-carbonitrile (**89**), obtained by the action of dimethylformamide and phosphoryl chloride on 4-amino-1-methyltriazole-5-carboxamide, furnished 6-amino-7-methyl-8-azapurine (87% yield) when refluxed with aqueous ammonium acetate (4 equiv) for 10 min. Ammonium chloride could not replace the acetate. The 2-methyl isomer of **89** reacted similarly; but the 3-methyl isomer (a much weaker base) reacted only slightly; lowering the pH to increase its ionization only accelerated hydrolysis of the amidino group. Methylamine acetate solution gave, with the nitrile **89**, 7-methyl-6-methylamino-8-azapurine (81% yield),⁵⁴ and butylamine acetate acted similarly (75% yield).⁷⁵

5-Cyano-4-ethoxymethylenamino-2-methyl-1,2,3-triazole (**90**), stirred at 0°C with ethanolic methylamine, gave an 87% yield of 1,6-dihydro-6-imino-1,8-dimethyl-8-azapurine; the 7-methyl isomer **55** and 9-benzyl isomer were similarly made.⁸⁷ Butylamine was used likewise to introduce a 1-butyl group.⁷⁵

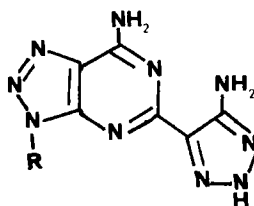
4-Dimethylaminomethylenamino-1-methyltriazole-5-carbonitrile (**89**), when refluxed (10 h) with ethanolic sodium hydrogen sulfide, gave 7-methyl-8-azapurine-6-thione (84% yield), and the 8-methyl isomer was similarly obtained.⁵⁴

4-Ethoxymethylenamino-2-methyl-1,2,3-triazole-5-carbonitrile (**90**) (also its 1-methyl and 3-benzyl analogs), when refluxed with ethanolic sodium hydrogen sulfide for 10 h, produced 8-methyl-, 7-methyl-, and 9-benzyl-8-azapurine-6-thione in 83–97% yields.⁸⁸ 4-Amino-1,2,3-triazole-5-carbonitrile and its 2-methyl and 9-benzyl derivatives were refluxed (2 h) with potassium *O*-ethylthiocarbonate in dimethylformamide (or alternatively with carbon disulfide in pyridine) to produce 8-azapurine-2,6-dithione (or its respective alkyl derivatives) in 88–95% yields.⁸⁸

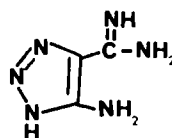
4-Amino-1-methyl-1,2,3-triazole-5-carbonitrile, when refluxed in pyridine with phenyl isothiocyanate, gave 6-anilino-7-methyl-8-azapurine-2-

thione (95% yield). The 8-methyl and 9-benzyl isomers were similarly prepared.⁸⁸

When 4-amino-3-benzyl-1,2,3-triazole-5-carbonitrile was refluxed with ethanolic potassium hydroxide, the dimer **91a** was isolated in 40% yield.¹⁷⁷ A similar dimer (**91b**) was produced by the action of phenyl azide on malononitrile.¹⁷¹

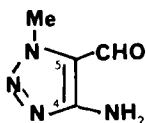


(91a) R = CH₂Ph
(91b) R = Ph²

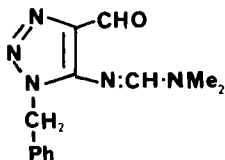


(92)

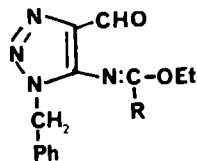
b. Syntheses from 5-Amidinotriazoles. 4-Amino-1,2,3-triazole-5-carboxamidine (**92**), when refluxed with triethyl orthoformate (7 h), furnished a 92% yield of 6-amino-8-azapurine.¹³⁶ The 3-benzyl analog, similarly treated with triethyl orthoacetate, gave 6-amino-9-benzyl-2-methyl-8-azapurine (83% yield).⁷⁶ That these should be the only two examples of this reaction could be because this type of starting material is, so far, available only by the ring opening of 6-amino-8-azapurines (see p. 150).



(93)



(94)



(95a) R = H
(95b) R = Me
(95c) R = OEt

c. Syntheses from Triazole Aldehydes. Syntheses from triazole aldehydes presented initial difficulties. The amino group of 4-aminotriazole-5-carbaldehydes, such as **93**, proved difficult to acylate, and the products resisted ring closure. Success followed the adoption of a conjugating side chain in the 4-position, as in **94** and **95**.¹¹⁹ Thus 4-amino-3-benzyl-1,2,3-triazole-5-carbaldehyde, stirred with dimethylformamide and phosphoryl chloride (20°C, 10 h), yielded 83% of 3-benzyl-4-dimethylaminomethylenamino-1,2,3-triazole-5-carbaldehyde (**94**). This, when refluxed with ammo-

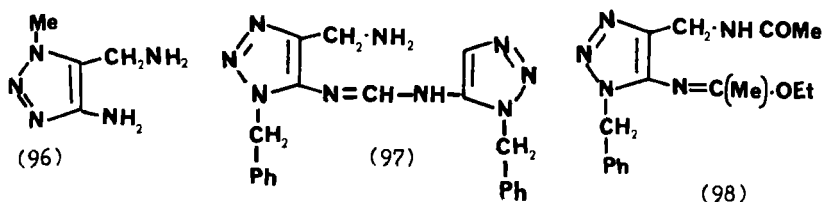
¹⁷⁷ A. Albert, *J. Chem. Soc. C*, 230 (1970).

nium acetate in methanol (8 h), produced 9-benzyl-8-azapurine (76% yield). The same 4-amino aldehyde, when refluxed (7 h) with triethyl orthoformate, yielded 82% of 3-benzyl-4-ethoxymethylenamino-1,2,3-triazole-5-carbaldehyde (95a), which, when stirred in ethanolic ammonia (20°C, 7 h), gave 9-benzyl-8-azapurine (74% yield). Triethyl orthoacetate similarly provided (via 95b) 9-benzyl-2-methyl-8-azapurine (40% for two steps). Likewise, tetraethyl orthocarbonate $[C(OEt)_4]$ produced (via 95c) 9-benzyl-2-ethoxy-8-azapurine (39% for 2 steps), which proved to be a versatile intermediate. 4-Amino-1-methyl- and -2-methyl-1,2,3-triazole-5-carbaldehydes also underwent these reactions.¹¹⁹

In somewhat related reactions, 4-diaminomethylenamino-5-(2-cyano-2-ethoxycarbonylvinyl)-1,2,3-triazole (43b), shaken with 0.5 *N* sodium hydroxide (20°C, 2 min), gave 2-amino-8-azapurine (72% yield) and ethyl cyanoacetate. The related substance 43a, when sublimed at 150°C, was quantitatively converted to 8-azapurine.⁶⁸

3. From Rings with an Amino Group Adjacent to an Aminomethyl Group; Synthesis of 1,6-Dihydro-8-azapurines

The 4-amino-5-aminomethyl-8-azapurines (e.g., 96), which were made by hydrogenating the 5-cyano analogs, provided a good approach to the synthesis of 1,6-dihydro-8-azapurines, stable substances whose oxidation (see p. 139) furnished 8-azapurines unsubstituted in the 6 position.

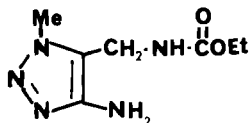


The first attempts to use these aminomethyl triazoles revealed that condensations with orthoesters were sensitive to small changes in conditions. To obtain any product at all, the starting triazole had to be present as a salt, but the nature of the anion governed the course of the reaction. The two best results were as follows. 4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazole hydrochloride and triethyl orthoformate, refluxed in ethanol (1 h), yielded 76% of 9-benzyl-1,6-dihydro-8-azapurine. For reaction with triethyl orthoacetate under similar conditions, only the acetate of the triazole gave 9-benzyl-2-methyl-1,6-dihydro-8-azapurine (65% yield). Yet, when the acetate of the triazole was condensed, as above, with triethyl orthoformate, only *N,N*-

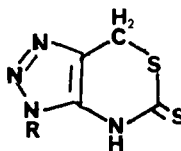
bis(5-aminomethyl-3-benzyl-1,2,3-triazol-4-yl)formamidine (**97**) was produced (90% yield). Finally, when the hydrochloride of the triazole was condensed with triethyl orthoacetate, the sole product was 5-acetamidomethyl-3-benzyl-4-(α -ethoxyethylidenamino)-1,2,3-triazole (**98**) (50% yield), which resisted cyclization.⁶¹

With some relief, it was found that replacement of orthoesters by amidines provided a reaction much less sensitive to conditions. Accordingly, the aminomethyl triazoles (**96**, and its 2-methyl and 3-benzyl analogs), as free bases, were refluxed in butanol with the acetates of formamidine, acetamidine, and trichloroacetamidine (1–4 h), to give 60–95% yields of the corresponding 1,6-dihydro-8-azapurines, which carried the characteristic group of the amidine in the 2 position. Thus **96** and trichloroacetamidine produced 7-methyl-2-trichloromethyl-1,6-dihydro-8-azapurine.⁶¹ With less avidity, a secondary amine, 4-amino-3-benzyl-5-methylaminomethyl-1,2,3-triazole, reacted with formamidine acetate in boiling butanol to give 9-benzyl-1,6-dihydro-1-methyl-8-azapurine, and the best yield of 80% could be reached only when a new portion of formamidine acetate was introduced at 2-hourly intervals.⁵

To obtain 2-amino-1,6-dihydro-8-azapurine, **96** (and its 2-methyl and 3-benzyl analogs) were refluxed with cyanogen bromide in methanol (4 h), giving 40–75% yields of the correspondingly alkylated products.⁵⁰ 4-Amino-5-ethoxycarbonylaminoethyl-1,2,3-triazole (**99**) (from **96** and ethyl chloroformate), when refluxed in butanolic sodium butoxide (1 h), produced 7-methyl-1,6-dihydro-8-azapurin-2-one; the 8-methyl and 9-benzyl analogs were made similarly (76–92% yield).⁵⁰



(99)



(100)

Finally, **96** (and its 2-methyl analog), when heated in pyridine with carbon disulfide and triethylamine (bath at 115°C, 6 h), yielded 95% of 7- and 8-methyl-1,6-dihydro-8-azapurine-2-thione.⁸² Derivatives of a new ring system were produced instead of azapurines when the 3-methyl and 3-benzyl analogs of **96** were treated similarly, giving 3-alkyl-3,7-dihydro-3H-1,2,3-triazolo[4,5-d]thiazine-5(4H)-thiones (**100**) in high yields.¹⁷⁸ Attempts to

¹⁷⁸ A. Albert, *J. C. S. Perkin I*, 2009 (1980); A. Albert and A. Dunand, *Angew. Chem., Intl. Ed. Engl.* **19**, 310 (1980).

prepare some 1,6-dihydro-8-azapurine-2-carboxamides from various oxalyl derivatives failed because of intramolecular rearrangements.⁸²

C. SOME HELP IN CHOOSING THE STARTING MATERIALS

The parent, 8-azapurine, has been made only by nitrosation of 4,5-diaminopyrimidine, which is an item of commerce.^{48,96,155} The 7- and 8-alkyl derivatives of 8-azapurine, whether with or without further substituents, require 1,2,3-triazole starting materials (Section IV,B), of which the best source is Hoover and Day's historic condensation of benzyl azide with ethyl cyanoacetate or (better) cyanoacetamide.¹⁶⁸ An 8-aryl group has been introduced similarly.⁷² In favorable cases, an 8-aryl group can be derived from the action of a benzenediazonium chloride on a pyrimidine that bears enough electron-releasing substituents to activate the 5 position (the Benson synthesis; Section IV,A).

A wider choice of starting materials is available for those 8-azapurines that have a 9-substituent. The relative merits of the pyrimidine and the triazole approaches have been discussed in ref. 59. To end with a 9-benzyl or a 9-phenyl substituent, the triazole approach has been found more straightforward and economical.^{167,168} Handled with care, benzyl and phenyl azides have been used, even on the kilogram scale. When using the triazole approach, it should be noted that each group present in the 5 position at the time of cyclization must originate in an ester or (preferably) an amide group at an earlier stage.

For a 9-methyl substituent, the triazole approach (although safely effected¹⁶⁷ with suitable precautions¹⁷⁹) is usually considered to be too dangerous because of the erratic detonating properties of methyl azide. This disadvantage can be circumvented by performing a Dimroth retrogression on the readily available⁵⁹ 4-methylamino-1,2,3-triazole-5-carboxamide (76a). When this is simply refluxed with pentanol for 1 h,⁶ the intermediate 4-amino-3-methyl-1,2,3-triazole-5-carboxamide is formed in 96% yield, and may be converted by formamide (220°C, 45 min) to the versatile 9-methyl-8-azapurin-6-one in 78% yield.² A similar stratagem to avoid the use of methyl azide is seen in the preparation of 6-amino-9-methyl-8-azapurine by refluxing 6-methylamino-8-azapurine with dimethylformamide for 14 h (72% yield).⁷⁵

For the synthesis of 9-glycosyl- and the related 9-cyclopentanyl-8-azapurines, see pp. 136, 157, and 163.

Of 8-azapurines unsubstituted in the triazole ring, the following are com-

¹⁷⁹ C. Grundmann, in "Houben-Weyls Methoden der organischen Chemie" (R. Stroh, ed.), Vol. 10, Part 3, p. 835. Thieme, Stuttgart, 1965.

mercially available: 8-azaadenine, -xanthine, -guanine, and -hypoxanthine. The last-named (8-azapurin-6-one) forms a sparingly soluble sodium salt with which the commercial material is often contaminated and from which it can be freed by boiling with pH 2.5 buffer.⁵⁹ 8-Azapurin-6-one is best prepared from 4-amino-1,2,3-triazole¹⁶⁸ and formamide.⁵⁹ Unfortunately, it does not undergo the usual metathetical changes; hence other 8-azapurines unsubstituted in the triazole ring are usually made by nitrosating 4,5-diaminopyrimidines.^{4,59} For difficulties encountered in preparing 8-azapurine-6-thione (and 9-substituted 8-azapurine-6-thiones), due to isomerism, see p. 154.

The preparation of 2-substituted 8-azapurines, unsubstituted in the triazole ring, from pyrimidines is described in ref. 48, and from triazoles (via 1,6-dihydro-8-azapurines) in Section IV,B,3. 8-Azapurines with strongly electron-attracting groups in either the 2 or the 6 position are unknown and may turn out to be unstable.

V. Biological and Industrial Applications

When Roblin and his colleagues synthesized⁴ 8-azaguanine (2-amino-8-azapurin-6-one) in 1945 and introduced it to biology, it was not suspected that this substance occurred in nature. However, in 1961, it was isolated as the antibiotic of a bacterium, *Streptomyces albus* (var. *pathocidicus*).¹⁸⁰ Initial scepticism that nature could assemble three linked nitrogen atoms, vanished when it was shown that this organism efficiently converted guanine-2-¹⁴C to similarly labeled 8-azaguanine. The nonincorporation of the label of guanine-8-¹⁴C revealed the pathway.¹⁸¹ In the commercial fermentative preparation,¹⁸² *Streptomyces* SF-337, when grown in aerated corn-steep liquor at pH 7 (28°C, 70 h), produced 0.8 g of 8-azaguanine per 250 L.¹⁸²

The principal applications for 8-azapurines have been found in cancer research and treatment, in oral medication for allergies (still at the clinical trial stage), antiviral research, and in phototechnology.

A. INVESTIGATIONS AIMED AT THE TREATMENT OF CANCER

8-Azaguanine was the first analog of purines found to be active against cancers in laboratory animals.¹⁸³ When 38 patients with inoperable tumors

¹⁸⁰ K. Anzai and S. Suzuki, *J. Antibiot., Ser. A* **14**, 253 (1961).

¹⁸¹ K. Hirasawa and K. Isono, *J. Antibiot.* **31**, 628 (1978).

¹⁸² T. Niida, K. Hamamoto, T. Tsuruoka, and K. Hara, Japanese Patent (67) 1478 (1964) [*CA* **66**, 74952 (1967)].

¹⁸³ L. W. Law, *Cancer Res.* **10**, 186 (1950); A. Gellhorn, M. Engelman, D. Shapiro, S. Graff, and H. Gillespie, *ibid.*, 170.

of the head were treated with localized intra-arterial infusions of 8-azaguanine, a 30% objective improvement was found.¹⁸⁴ This treatment was based on the discovery that tumors are usually lacking in guanase, whereas healthy human brain tissue is rich in this enzyme, which converts the drug to biologically inert 8-azaxanthine.¹⁸⁵ Unfortunately, clinical improvement could not be maintained without repeating the treatment, and some side effects appeared.¹⁸⁴ The search for a more selective 8-azapurine anticancer drug continues unabated as the following sections show. In tumor-bearing mice, 8-azaguanine is phosphoribosylated, then incorporated into t- and mRNA, but not into DNA.¹⁸⁶ From this vantage point, it exercises its inhibition of protein synthesis, and hence its cytotoxicity. Because 8-azapurines are not incorporated into DNA, the risk of causing mutation, which is presented by most purine and pyrimidine analogs, is avoided. The 8-azapurines are also providing useful tools for the molecular biologist. The inhibition by 8-azaguanine of the growth of microorganisms is competitively reversed by guanine.¹⁸⁷

For reviews, see refs. 188 (8-azapurines) and 189 (8-azaguanine).

1. *Studies in Mammals*

8-Azaguanine brought about a 60% increase in the lifespan of mice with leukemia L1210. However, its ribonucleoside was inactive because it did not become phosphorylated,¹⁹⁰ whereas 8-azaguanine was transformed by HPRT (hypoxanthine phosphoribosyltransferase) into its nucleotide, which RNA can incorporate.¹⁹¹ On the other hand, 8-azaadenosine^{192,193} and 8-azainosine (9-ribofuranosyl-8-azahypoxanthine),^{192,194} both of which dis-

¹⁸⁴ T. C. Hall, M. J. Krant, J. B. Lloyd, W. B. Patterson, A. Ishihara, K. G. Potee, T. O. Lovina, and J. M. Miller, *Cancer (N.Y.)* **15**, 1156 (1962).

¹⁸⁵ R. J. Levine, T. C. Hall, and C. A. Harris, *Cancer (N.Y.)* **16**, 269 (1963); E. Hirschberg, M. R. Murray, E. R. Peterson, J. Kream, R. Schafranek, and J. L. Pool, *Cancer Res.* **13**, 153 (1953).

¹⁸⁶ J. H. Mitchell, H. E. Skipper, and L. L. Bennett, *Cancer Res.* **10**, 647 (1950); H. G. Mandel, P. E. Carló, and P. K. Smith, *J. Biol. Chem.* **206**, 181 (1954).

¹⁸⁷ G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, and H. VanderWerff, *Ann. N.Y. Acad. Sci.* **52**, 1318 (1950).

¹⁸⁸ R. E. Parks and K. C. Agarwal, *Handb. Exp. Pharmacol.* **38**, 458 (1975).

¹⁸⁹ D. Grunberger and G. Grunberger, *Antibiotics (N.Y.)* **5**, 110 (1979).

¹⁹⁰ J. A. Montgomery, F. M. Schabel, and H. E. Skipper, *Cancer Res.* **22**, 504 (1962).

¹⁹¹ R. S. Rivest, D. Irwin, and H. G. Mandel, *Biochem. Pharmacol.* **31**, 2505 (1982).

¹⁹² J. A. Montgomery, R. D. Elliott, and H. J. Thomas, *Ann. N.Y. Acad. Sci.* **255**, 292 (1975).

¹⁹³ R. D. Elliott and J. A. Montgomery, *J. Med. Chem.* **20**, 116 (1977).

¹⁹⁴ L. L. Bennett, M. H. Vail, P. W. Allan, and W. R. Laster, *Cancer Res.* **33**, 465 (1973).

play strong activity against leukemias L 1210 and P 388 in mice, are directly metabolized to the 5'-triphosphates, which are incorporated into RNA. The situation is complicated by the conversion of 8-azaadenosine (by adenosine deaminase) to 8-azainosine. Moreover, the ribotide 8-azainosinic acid is partly metabolized to 8-azaadenylic and 8-azaguanylic acids.^{192,195}

The carcinostatic action of 8-azaguanine against the Ehrlich ascites tumor in mice was potentiated by 4-aminoimidazole-5-carboxamide, which exerted a synergistic effect by preventing deamination.¹⁹⁶ The toxicity exerted by 8-azaadenosine in mice was traced to its 5'-triphosphate, which replaced adenosine triphosphate in the host's hepatocytes.¹⁹⁷ Phosphatidylcholine liposomes were studied as a suitable vehicle for conveying 8-azaguanine to leukemic cells.¹⁹⁸

The 9-trihydroxycyclopentyl derivative of 8-azaadenine, a carbocyclic analog of 8-azaadenosine, proved active against leukemia P388 in the mouse.¹⁹⁹

2. Cell-Culture Studies

8-Azahypoxanthine prevented cloning of human malignant HeLa S3 cells, but not of normal human cells, whereas 8-azaadenine prevented cloning of either type.²⁰⁰ 8-Azainosine (1 μ M) inhibited colony formation by human epidermoid (type 2) carcinoma cells in culture.¹⁹³ In cell-free extracts of HeLa cells, protein synthesis was inhibited by the incorporation of 8-azaguanine into the mRNA of polysomes, in which it blocked formation of peptide bonds.²⁰¹

Unlike 6-mercaptopurine and 6-thioguanine, 8-azaguanine diffused into Novikoff hepatoma cells (rat) without any sign of saturability, indicating that no carrier was involved. By varying the pH, it was shown that only the nonionized form entered the cell.²⁰² 9- α -D-Arabinofuranosyl-8-azaadenine was found toxic to human epidermoid carcinoma cells in culture, whereas

¹⁹⁵ L. L. Bennett and P. W. Allan, *Cancer Res.* **36**, 3917 (1976).

¹⁹⁶ H. Nishio, I. Yamamoto, K. Kariya, and K. Hano, *Chem. Pharm. Bull.* **17**, 539 (1969).

¹⁹⁷ E. N. Spremulli, G. W. Crabtree, D. L. Dexter, H. S. Chu, D. M. Farineau, L. Y. Ghoda, D. L. McGowan, I. Diamond, R. E. Parks, and P. Calabresi, *Biochem. Pharmacol.* **31**, 2415 (1982).

¹⁹⁸ J. H. Fendler and A. Romero, *Life Sci.* **18**, 1453 (1976).

¹⁹⁹ R. Vince, J. Brownell, and S. Daluge, *J. Med. Chem.* **27**, 1358 (1984).

²⁰⁰ M. H. Vaughan and M. W. Steele, *Exp. Cell Res.* **69**, 92 (1971).

²⁰¹ E. F. Zimmerman, *Biochim. Biophys. Acta* **157**, 378 (1968).

²⁰² P. G. W. Plagemann, R. Marz, R. M. Wohlhueter, J. C. Graff, and J. M. Zylka, *Biochim. Biophys. Acta* **647**, 49 (1981).

the β anomer was not injurious. The α anomer was phosphorylated by adenosine kinase before it acted; it was not a substrate for adenosine deaminase.²⁰³ 8-Azaadenosine inhibited the biophosphorylation of 2-fluoroadenosine and hence permitted human lymphocytes to perform the cytolyses that 2-fluoroadenylic acid would otherwise have prevented.²⁰⁴

3. Biochemical Studies

When *Bacillus cereus* was grown in the presence of 8-azaguanine, an accumulation of submethylated ribonucleoprotein particles was observed.²⁰⁵ Enzymatic deamination of 8-azaadenosine could be greatly decreased by inserting a halogen into the 2 position.¹²¹

Although 9-ribofuranosyl-8-azapurine-6-thione ("azathioinosine"), which has a pK_a of 6.75, was a good substrate for the phosphorylating action of adenosine kinase, several analogous substances were not, because they were weaker acids.²⁰⁶ The Christmas-rearrangement product (a thiadiazolopyrimidine, see p. 154) from this thione was also a substrate for adenosine kinase, but neither heterocycle acted as a substrate for purine nucleoside phosphorylase. For human epithelioma (type 2) cells in culture, the 50% inhibitory concentrations of these substances were 0.14 and 1.8 μM , respectively. No incorporation into RNA or DNA occurred, but the two compounds inhibited synthesis of both nucleic acids. Azathioinosine inhibited synthesis of purine and pyrimidine nucleotides, and both compounds selectively reduced the pool of guanine nucleotides in human epithelioma cells.²⁰⁷

6-Methoxy-, 6-ethoxy-, and 6-methylthio-9-ribofuranosyl-8-azapurines turned out to be substrates for adenosine kinase, and the first two examples were bound by adenosine deaminase. Their cytotoxic action was attributed to affinity for the kinase.²⁰⁸ 6-Imino-9-phenyl-1,6-dihydro-8-azapurine was found to be an efficient inhibitor of adenosine deaminase and guanine deaminase. Xanthine oxidase was inhibited by both this compound and 9-aryl-8-azapurin-6-ones.²⁰⁹

²⁰³ L. L. Bennett, P. W. Allan, D. L. Hill, J. H. Thomas, and J. W. Carpenter, *Mol. Pharmacol.* **12**, 242 (1976).

²⁰⁴ T. P. Zimmerman, G. Wolberg, G. S. Duncan, J. L. Rideout, L. M. Beauchamp, T. A. Krenitsky, and G. B. Elion, *Biochem. Pharmacol.* **27**, 1731 (1978).

²⁰⁵ I. Votruba and D. Grunberger, *Collect. Czech. Chem. Commun.* **34**, 295 (1969).

²⁰⁶ L. L. Bennett, D. L. Hill, and P. W. Allan, *Biochem. Pharmacol.* **27**, 83 (1978).

²⁰⁷ L. L. Bennett, L. M. Rose, P. W. Allan, D. Smithers, D. J. Adamson, R. D. Elliott, and J. A. Montgomery, *Mol. Pharmacol.* **16**, 981 (1979).

²⁰⁸ L. L. Bennett, P. W. Allan, R. D. Elliott, and J. A. Montgomery, *Biochem. Pharmacol.* **28**, 946 (1979).

²⁰⁹ A. Lucacchini, L. Bazzichi, G. Biagi, O. Livi, and D. Segnini, *Ital. J. Biochem.* **31**, 153 (1982).

6-Chloro-9-cyclopentyl-8-azapurine inhibited synthesis of DNA, RNA, and protein in *E. coli*. Blockage of thymine–nucleotide formation was the first effect seen. Alkylation of enzymes by the 6-chloro substituent was suggested as a mechanism.²¹⁰ This azapurine inhibited the RNA polymerase from *E. coli*, but not that from *M. lysodeikticus*. Formyltetrahydrofolate synthetases, of both mammalian and bacterial origins, were strongly inhibited.²¹¹ The same azapurine, at 0.3 mM, markedly inhibited the steroid-induced synthesis of Δ^5 -3-ketosteroid isomerase in *Pseudomonas testosteroni*.²¹²

8-Azapurines were found to be good substrates for xanthine oxidase (from milk), which inserted oxygen atom(s) into the 2 and/or 6 position(s) when these were free. The rates achieved were from 3 to 41% that of xanthine.¹⁵⁵

The presence of the nitrogen atom in the 8 position of 8-azapurines lowers the barrier to rotation of a 9-glycosyl substituent. An X-ray diffraction study of 8-azaadenosine revealed a torsion angle of 104° in contrast to the 15° of adenosine. It was maintained that this large difference could alter coding and base-pairing when the 8-azapurine replaced a purine residue in RNA.²¹³

8-Azaadenine and -guanine (also their ribosides) were 5'-triphosphorylated to ribotides by incubation with a culture of *Brevibacterium ammoniagenes*.²¹⁴

4. Drug Resistance, Mutations

Lines of leukemia cells, which had become resistant to 8-azaguanine in the patient, during treatment, remained sensitive to 8-azaadenine.²¹⁵ Resistance to 8-azaguanine in the cancer-bearing mouse,²¹⁶ and in L929 leukemia cells,²¹⁷ was shown to arise from loss of the enzyme hypoxanthine–guanine phosphoribosyltransferase. This was not an induced deletion but the outgrowth of a minor (resistant) fraction of the malignant cell population.^{216,217} Two other sources of resistance to 8-azaguanine were indicated.²¹⁷

Resistance to 8-azaguanine has also been elicited, in several ways, in the

²¹⁰ M. S. Zedeck, A. C. Sartorelli, J. M. Johnson, and R. W. Ruddon, *Mol. Pharmacol.* **5**, 263 (1969).

²¹¹ R. W. Ruddon, C. H. Rainey, and M. S. Zedeck, *FEBS Lett.* **7**, 119 (1970).

²¹² M. S. Zedeck, A. C. Sartorelli, P. K. Chang, K. Raska, R. K. Robins, and A. D. Welch, *Mol. Pharmacol.* **3**, 386 (1967).

²¹³ D. J. Hodgson and P. Singh, in "Environmental Effects on Molecular Structure and Properties" (B. Pullman, ed.), p. 343. Reidel Publ., Dordrecht, Netherlands, 1976.

²¹⁴ H. Tanaka and K. Nakayama, *Agric. Biol. Chem.* **36**, 464 (1972).

²¹⁵ D. Adomaitiene, T. N. Ignatova, D. Ya. Podgaetskaya, and V. A. Gershun, *Tsitologiya* **12**, 457 (1970) [*CA* **73**, 23694 (1970)].

²¹⁶ J. Morrow, *Genetics* **65**, 279 (1970).

²¹⁷ O. P. Van Diggelen, T. F. Donahue, and S.-I. Shin, *J. Cell. Physiol.* **98**, 59 (1979).

complete absence of 8-azaguanine. Caffeine was found to decrease both the spontaneously arising and the ultraviolet-radiation-enhanced strains resistant to 8-azaguanine in hamster cells.²¹⁸ Resistance to this drug has been induced in Chinese hamster-cell cultures by *N*-methyl-*N*-nitroso-*N'*-nitroguanine²¹⁹ or simply by gamma-ray irradiation.²²⁰ Both hamster and human cells, in culture, have occasionally, but spontaneously, produced mutants resistant to 8-azaguanine.²²¹

As an alternative to the much-used Ames test for mutagenicity, forward mutation to 8-azaguanine resistance is being used as a more positive, and equally sensitive, alternative to the usual reverse mutation to histidine utilization.²²²

B. INVESTIGATIONS AIMED AT TREATING ALLERGIES

At least 85% of all cases of asthma appear to have an allergic basis. The outlook for patients suffering from this (usually) lifelong disability was brightened in 1968 by the introduction of disodium cromoglycate (cromolyn, "Intal"), the first prophylactic found for the asthmatic condition. This drug (the salt of a benzopyrone-2-carboxylic acid) acts by preventing the escape of histamine and the more powerfully acting (and longer lasting) leukotrienes (prostaglandin peptides) from the mast cells and lymphocytes of the patient's lungs. Unfortunately, this drug has to be administered by insufflation of the powder, which is messy, often inconvenient, and does not control the dose. Hence the current search for a therapeutically similar but orally active substance. It is currently thought²²³ that such a drug requires a flat, preferably heterocyclic, nucleus with a fully ionized (at pH 7) acidic center near a carbonyl group. The latter may form part of an amide, lactam, vinylogous lactam, or of the corresponding lactones. In addition, a small area offering steric hindrance has been indicated as valuable (ref. 223, p. 81).

Progressive modification of the structure of theophylline and other methylxanthines led to 8-azapurine analogs^{224,225} and from there, eventually, to

²¹⁸ J. E. Trusko and E. H. Y. Chu, *Mutat. Res.* **12**, 337 (1971).

²¹⁹ D. Wild, *Mutat. Res.* **25**, 229 (1974).

²²⁰ C. F. Arlett and J. Potter, *Mutat. Res.* **13**, 59 (1971).

²²¹ N. I. Shapiro, A. E. Khalizev, E. V. Luss, M. I. Marshak, O. N. Petrova, and N. B. Varshaver, *Mutat. Res.* **15**, 203 (1972).

²²² T. R. Skopek, H. L. Liber, D. A. Kaden, and W. G. Thilly, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 4465 (1978).

²²³ E. Lunt, *Prog. Pharm. Chem.* **4**, 41 (1983).

²²⁴ C. J. Coulson, R. E. Ford, E. Lunt, S. Marshall, D. L. Pain, I. H. Rogers, and K. R. H. Wooldridge, *Eur. J. Med. Chem.* **9**, 313 (1974).

²²⁵ A. Holland, D. Jackson, P. Chaplen, E. Lunt, S. Marshall, D. L. Pain, and K. R. H. Wooldridge, *Eur. J. Med. Chem.* **10**, 447 (1975).

2-*o*-propoxyphenyl-8-azapurin-6-one (M & B 22,948, zaprinast) (**12**) which, in three types of asthma-simulating laboratory tests, proved to be 20–50 times more potent than disodium cromoglycate, and it was also orally active.^{30,226} The heightened antiallergic activity of **12** is derived from an extended flat area provided by coplanarity of the phenyl group with the azapurine ring, a coplanarity favored by hydrogen bonding between the H-1 of the heterocyclic nucleus and the oxygen of the propoxy group.³⁰ Some X-ray crystallographic studies were reviewed in Section II,A. Syntheses of these and related structures are described in refs. 30, 173, and 227. Reference 227 demonstrates the chemical and biological possibilities of amino substituents when placed para to the propoxy group of **12**.

Both the 8-azapurine **12** and disodium cromoglycate inhibit mast cells and lymphocytes from discharging their leukotrienes by two mechanisms: (i) they stabilize the plasma membrane of these cells, and (ii) they inhibit the phosphodiesterase that hydrolyzes cyclic GMP while little affecting the phosphodiesterase that hydrolyzes cyclic ATP.^{228,229} In the clinic, 5 mg of **12**, administered as an aerosol, prevented allergic bronchospasm in asthmatic patients.²³⁰ The 9-phenyl-8-azapurines discussed in Section IV,B,1 (p. 163) also have antiallergic properties.^{126a}

C. ANTIVIRAL STUDIES

Useful antiviral properties were shown by 2-amino-9-(2-hydroxyethoxy)methyl-8-azapurin-6-one, the azapurine analog of the purine antiviral drug acyclovir, which is much used in treating human herpes.²³¹ 9-(2-Hydroxy-4-hydroxymethylcyclopentyl)-8-azaadenine and -hypoxanthine were found to be potent inhibitors of herpes simplex virus (type 1 only) *in vitro*.¹⁴⁷

6-Amino-9- α -D-arabinofuranosyl-8-azapurine showed strong antiviral action *in vitro* against seven virus species.⁷¹ However, it proved ineffective against lethal herpes virus infections in mice²³² and against several other

²²⁶ B. J. Broughton, P. Chaplen, P. Knowles, E. Lunt, D. L. Pain, K. R. H. Wooldridge, R. Ford, S. Marshall, J. L. Walker, and D. R. Maxwell, *Nature (London)* **251**, 650 (1974).

²²⁷ German Patent 2,747,199 (1978) [CA **89**, 24359 (1978)], to May and Baker, Ltd.

²²⁸ C. J. Coulson, R. E. Ford, S. Marshall, J. L. Walker, K. R. H. Wooldridge, K. Bowden, and T. J. Coombes, *Nature (London)* **265**, 545 (1977).

²²⁹ H. Bergstrand, J. Kristofferson, B. Lundquist, and A. Schurman, *Mol. Pharmacol.* **13**, 38 (1977); R. Weishaar, M. Cain, and J. Bristol, *J. Med. Chem.* **28**, 537 (1985).

²³⁰ J. Evans, R. E. Ford, P. F. Leswell, S. M. Marshall, and J. L. Walker, *Br. J. Pharmacol.* **70**, 177 P (1980).

²³¹ U.S. Patent 4,027,025 (1977) [CA **87**, 85045 (1977)], to H. Schaeffer and Burroughs Wellcome & Co.

²³² L. L. Bennett, P. W. Allan, S. C. Shaddix, W. M. Shannon, G. Arnett, L. Westbrook, J. C. Drach, and M. C. Reinke, *Biochem. Pharmacol.* **30**, 2325 (1981).

viruses *in vitro*.²³³ 8-Azaguanine lowered the titer of smallpox virus, measured as plaque-forming capacity, but its cytopathic activity in chick-embryo culture remained unchanged.²³⁴

8-Azaguanine-resistant avian sarcoma virus-infected cells were less tumorigenic than nonresistant cells in hamsters.²³⁵ Incubation of cells (infected with adenoviruses in tissue culture) with 8-azaguanine (10^{-4} M) inhibited reproduction of the virus. At this concentration, the drug was not toxic for healthy mammalian cells.²³⁶

8-Azaguanine (0.25 mg/ml) decreased protein synthesis in pig-kidney cells infected with the virus of foot-and-mouth disease, but virus replication was not affected.²³⁷ 8-Azaguanine delayed the onset of encephalomyocarditis virus growth and slowed the rate in mouse L-cell tissue cultures, an effect independent of the synthesis of macromolecules by the host cell.²³⁸

8-Azaadenine (1 mg/L) inhibited potato X-virus reproduction and infectivity in *Datura stramonium*.²³⁹ Weekly spraying with 0.1% 8-azaguanine prevented leaf-curl virus infection in tomatos; a significant increase in growth and yield of the plants ensued.²⁴⁰

D. MISCELLANEOUS BIOLOGICAL INVESTIGATIONS (PHARMACOKINETICS, AGRICULTURE, PROTECTION FROM RADIATION)

An ointment consisting of 6-chloro-9-cyclopentyl-8-azapurine in soft paraffin is used for treating psoriasis; derivatives and analogs are also claimed.²⁴¹ Several 1,3-dimethyl-8-azapurine-2,6-diones bearing a further substituent

²³³ J. A. Montgomery, A. T. Shortnacy, G. Arnett, and W. M. Shannon, *J. Med. Chem.* **20**, 401 (1977).

²³⁴ G. A. Chaiko, V. A. Sevast'yanova, I. N. Fedotova, and G. A. Korolenko, *Tr. Tomsk. Nauchno-Issled. Inst. Vaksyn Syvorotok Tomsk. Med. Inst.* **26**, 106 (1975) [*CA* **86**, 165816 (1977)].

²³⁵ M. Hladka and C. Altaner, *J. Natl. Cancer Inst. (U.S.)* **53**, 1221 (1974).

²³⁶ V. P. Chernetcki and A. P. Starcheus, *Mikrobiol. Zh. (Kiev)* **34**, 30 (1972) [*CA* **77**, 1172 (1972)].

²³⁷ N. Z. Khazipov, *Uch. Zap. Kazan. Vet. Inst. im. N.E. Baumand* **105**, 77 (1969) [*CA* **76**, 108620 (1972)].

²³⁸ P. Balduzzi and A. Sherman, *Proc. Soc. Exp. Biol. Med.* **123**, 408 (1966).

²³⁹ I. P. Zhuk, L. F. Didenko, and N. I. Gorbarenko, *Biol. Nauki*, 108 (1970).

²⁴⁰ J. P. Varma, *Indian J. Exp. Biol.* **15**, 408 (1977).

²⁴¹ South African Patents 01,997 and 01,998 (1978) [*CA* **89**, 163593 and 180033 (1978)], to Sherico AG.

in the 7 position had strong vasodilating properties, although inferior to those of theophylline.²⁴²

8-Azaguanine inhibited the development of tolerance in mice to the analgesic effect of morphine.²⁴³ Kits for the clinical measurement of guanase, the most sensitive of all tests for liver damage, consisted of 8-azaguanine in bis(hydroxyethyl)glycine buffer. The evolved ammonia was measured colorimetrically.²⁴⁴

9-Furfuryl-8-azapurine was found to be 100 times as potent as theophylline in inhibiting the cyclic phosphodiesterase of lipocytes and in potentiating the stimulation of lipolysis.²⁴⁵ 8-Azaguanine (25 mg/kg), given subcutaneously daily for 5 days, inhibited production of precipitins during immunization of the rabbit with bovine serum albumin. This heterocycle also decreased the number of antibody-forming cells in mouse spleen.²⁴⁶

Plants poisoned with 8-azaguanine showed increased RNase activity and morphological changes reminiscent of boron deficiency.²⁴⁷ A single soaking of the tubers of chufa (an edible plant, *Cyperus esculentus*) in aqueous 8-azaguanine stimulated growth and development of the plant and increased the yield of nodules for the next 3 years.²⁴⁸ Azaadenine (50 µg/L) inhibited biosynthesis of ATP in *Neurospora crassa*.²⁴⁹ 2-Ethyl-9-(*p*-chlorobenzyl)-8-azapurin-6-one and analogs displayed strong fungicidal activity.^{249a}

A dose of 64 mg/kg of 8-azaxanthine, given 2 h before exposure to radiation (700 rads), effected 24% survival whereas all the control mice died.²⁵⁰ 1,3,9-Trimethyl-8-azaxanthine, at 350 mg/kg intraperitoneally, saved 25% of mice subjected to X-radiation lethal to all controls.²⁵¹ 6-Amino-2-thioxo-, -2-methylthio-, and -2-ethylthio-8-azapurine had significant radioprotective properties, lost on quaternization.²⁵²

²⁴² D. S. Bariana, *J. Med. Chem.* **14**, 543 (1971).

²⁴³ I. Yamamoto, R. Inoki, Y. Tamari, and K. Iwatsubo, *Jpn. J. Pharmacol.* **17**, 140 (1967).

²⁴⁴ S. Ito, T. Takaoko, H. Mori, and A. Teruo, *Clin. Chim. Acta* **115**, 135 (1981).

²⁴⁵ M. Chasin, F. Mamrak, K. Koshelnyk, and M. Rispoli, *Arch. Int. Pharmacodyn. Ther.* **227**, 180 (1977).

²⁴⁶ B. S. Uteshev, B. V. Pinegin, A. G. Kalinkovich, and V. V. Lebedev, *Farmakol. Toksikol (Moscow)* **32**, 308 (1969).

²⁴⁷ M. Ya. Shkol'nik and Y. S. Smirnov, *Tr. Bot. Inst., Akad. Nauk SSSR, Ser. 4* **20**, 45 (1970) [*CA* **74**, 28976 (1971)].

²⁴⁸ N. P. Denisova, *Fiziol. Fiz.-Khim. Mekh. Regul. Obmennykh Protssessov Org.* **2**, 19 (1973).

²⁴⁹ H. Urbaneck, *Acta Soc. Bot. Pol.* **36**, 347 (1967).

^{249a} F. E. Nielsen, E. B. Petersen, and M. Begtrup, *Justus Liebigs Ann. Chem.*, 1848 (1984).

²⁵⁰ V. I. Svatkov, *Gig. Sanit.* **33**, 96 (1968) [*CA* **70**, 26187 (1969)].

²⁵¹ G. N. Krutovskikh, A. M. Rusanov, G. F. Gornaeva, L. P. Vartanyan, M. R. Kolesova, Kh. L. Muravich-Alexsandr, N. R. Smirnova, and S. S. Cherkazova, *Khim.-Farm. Zh.* **11**, 82 (1977) [*CA* **86**, 182955 (1977)].

²⁵² G. N. Krutovskikh, G. F. Gornaeva, L. P. Vartanyan, M. B. Kolesova, and N. V. Smirnova, *Khim.-Farm. Zh.* **18**, 325 (1984) [*CA* **101**, 38420 (1984)].

E. PHOTOTECHNOLOGY

2-Methyl-8-azapurin-6-one, a photographic image stabilizer, was studied for its physical properties and behavior with silver salts.²⁵³

8-(4-Styrylphenyl)-8-azapurin-6-ones, with or without substituents in one or both rings, were claimed as effective fluorescent whitening agents for cellulose acetate textiles.²⁵⁴ 8-Azapurines, with an 8-phenyl substituent (which may be further substituted) and a secondary or tertiary amino group in both 2 and 6 positions, are said to be good fluorescent whiteners for acetate fibers, polyamide fibers, and PVC films.²⁵⁵ 2-Dimethylamino-6-methoxy-8-(4-methoxyphenyl)-8-azapurine is claimed as an excellent fluorescent whitener for polyester, acrylic, acetate, and polyamide fibers, and for PVC films.²⁵⁶

Photolysis of 2,8-dimethyl- and 9-benzyl-2-methyl-8-azapurine, in water, gave 58 and 38%, respectively, of the 6-oxo derivative.²⁵⁷

²⁵³ G. P. Faerman and M. I. Fainshtein, *Trans. Leningr. Inst. Kinoizh.* **12**, 21 (1967) [*CA* **70**, 72955 (1969)].

²⁵⁴ German Patent 2,129,855 (1971) [*CA* **76**, 128833 (1972)], to A. F. Strobel and M. L. Whitehouse.

²⁵⁵ German Patent 2,749,902 (1978) [*CA* **89**, 112428 (1978)], to Ciba-Geigy A.-G.

²⁵⁶ German Patent 3,001,424 (1980) [*CA* **94**, 123120 (1981)], to Ciba-Geigy A.-G.

²⁵⁷ F. Kazmierczak, *Pol. J. Chem.* **54**, 1333 (1980) [*CA* **94**, 64853 (1981)].

Application of Aziridines to the Synthesis of Natural Products

TETSUJI KAMETANI AND TOSHIO HONDA

Institute of Medicinal Chemistry, Hoshi University, Tokyo, Japan

I. Introduction	182
II. Syntheses of Isoquinoline Alkaloids	182
A. Utilizing Ethylenimine	182
1. Crinine	182
2. Sendaverine and Corgoine	184
3. Reframidine	186
4. α -Dihydrocaranone and γ -Lycorane	189
5. Erythrinan Alkaloid	192
B. Utilizing Diazo Compounds	192
1. Reframidine	192
2. Cherylline	197
3. Cordrastine and Hydrastine	198
4. Morphinan Alkaloids	199
C. Others	205
1. Ochrobirine and Fumaricine (Ochotencine Alkaloids)	205
2. (\pm)- <i>cis</i> -Alpinigenine, (\pm)- <i>cis</i> -Alpinine, and (\pm)-Fumaritrine (Rheadan Alkaloids)	208
3. Lahorine and Lahoramine	210
III. Syntheses of Indole Alkaloids	213
A. Tryptamine and Its Derivatives	213
B. Dasycarpidone and Epidasycarpidone	215
C. Ibogamine and Coronaridine	217
IV. Miscellaneous	222
A. Serratinine	222
B. Diterpene Alkaloids	225
C. Pyrrolizidine Alkaloids	228
D. Mitomycin	230
E. β -Lactam	231
F. Muscazone	232
G. (\pm)-Pseudoconhydrine	232
H. Aspergillomarasmine A and B	235

I. Introduction

Aziridine, first synthesized by Gabriel in 1888,¹ is a well-known three-membered heterocycle containing a nitrogen atom, whose physicochemical properties have long been studied.²⁻⁵ The outstanding characteristic of aziridine is its high reactivity to a wide variety of both electrophilic and nucleophilic reagents to give the more stable ring-opened or ring-expanded amines, a property that stems from the release of the strain energy inherent in a small ring.

This review summarizes the application of aziridines as intermediates to the synthesis of natural products that do not contain an aziridine ring.

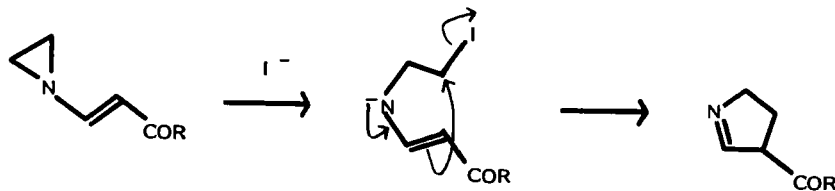


II. Syntheses of Isoquinoline Alkaloids

A. UTILIZING ETHYLENIMINE

1. *Crinine*

The synthesis of crinine, one of the Amaryllidaceae alkaloids, has been achieved by Whitlock⁶ and is based on an iodide ion-catalyzed rearrangement of *N*-ketovinylaziridines to Δ^1 -pyrroline (Scheme 1).^{7,8}



SCHEME 1

¹ S. Gabriel, *Chem. Ber.* **21**, 1049, 2664 (1888).

² R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds." Wiley (Interscience), New York, 1960.

³ R. Livingstone, in "Rodd's Chemistry of Carbon Compounds" (S. Coffey, ed.), Vol. IVA, p. 1. Elsevier, Amsterdam, 1973.

⁴ P. E. Fanta, *Chem. Heterocycl. Comp.* **19**, Part 1, 524 (1964).

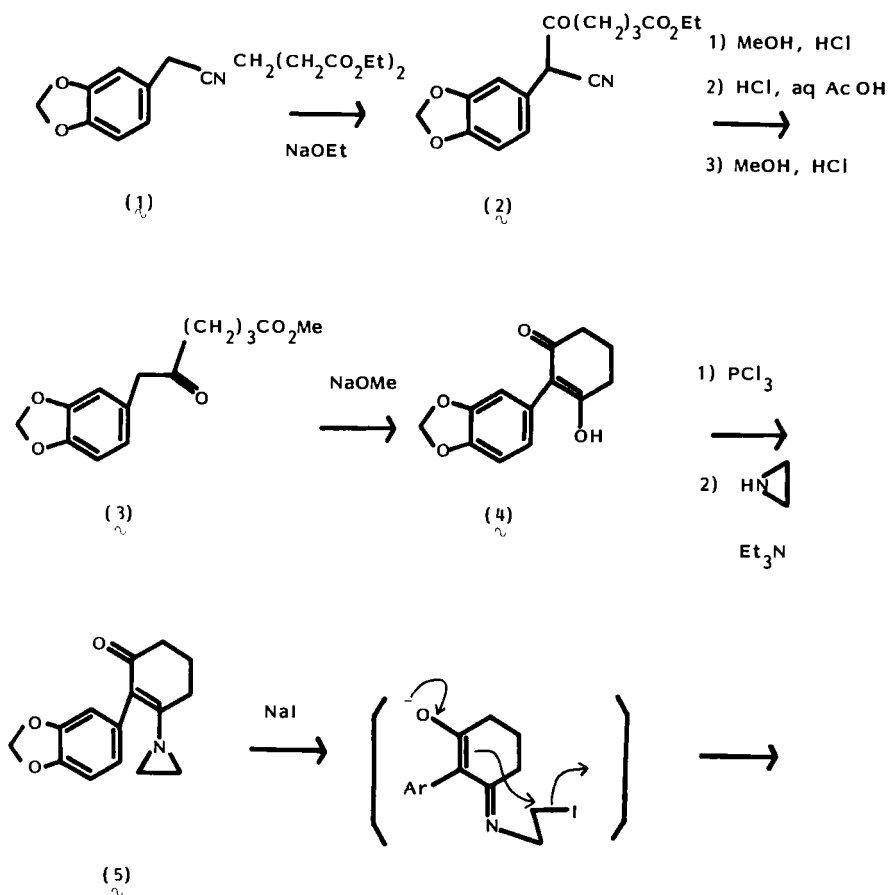
⁵ J. A. Deyrup, *Chem. Heterocycl. Comp.* **42**, Part 1, 1 (1983).

⁶ H. W. Whitlock and G. L. Smith, *J. Am. Chem. Soc.* **89**, 3600 (1967).

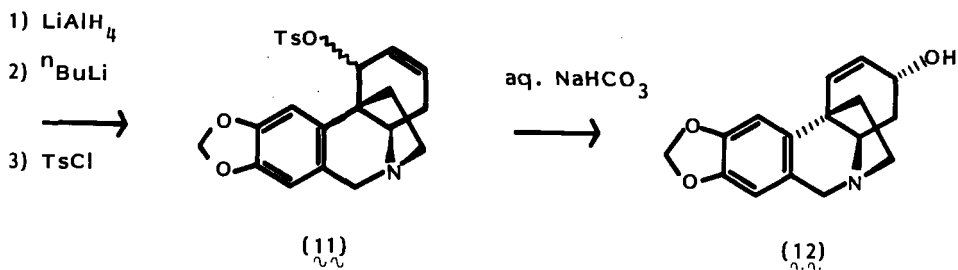
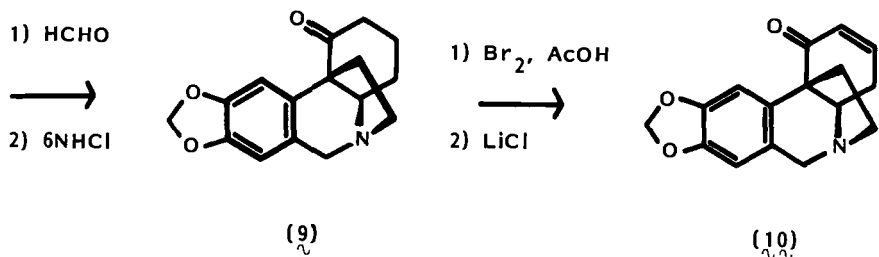
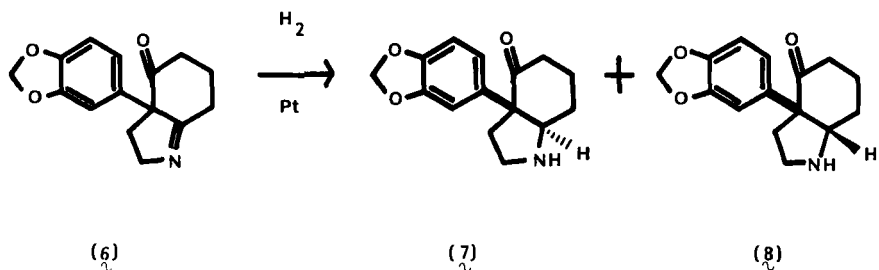
⁷ H. W. Whitlock and G. L. Smith, *Tetrahedron Lett.*, 1389 (1965).

⁸ H. W. Heine, *J. Am. Chem. Soc.* **85**, 2743 (1963).

The starting material was prepared by condensation of 3,4-methylenedioxybenzyl cyanide (**1**) with diethyl glutarate in ethanol in the presence of sodium ethoxide; the keto cyanide **2** was further converted to the keto ester **3** by subsequent methanolysis, hydrolysis, decarboxylation, and esterification. Intramolecular cyclization of the ester **3** gave the 1,3-cyclohexanedione **4** whose treatment with PCl_3 followed by ethylenimine yielded the aziridine derivative **5**. Rearrangement of **5** with iodide ion, as described above, brought about the formation of the Δ^1 -pyrroline derivative **6**, in 55% yield. In order to complete the synthesis, **6** was hydrogenated over a platinum catalyst to give a mixture of the *trans*-**7** (5.5%) and *cis*-**8** derivatives (76%). Mannich reaction of the latter (**8**) led to the formation of the crinane skeleton (**9**), which on 1,3 transposition of the oxygen function, as outlined in Scheme 2, gave crinane (**12**), via **10** and **11**.



SCHEME 2



SCHEME 2 (continued)

2. Sendaverine and Corgoine

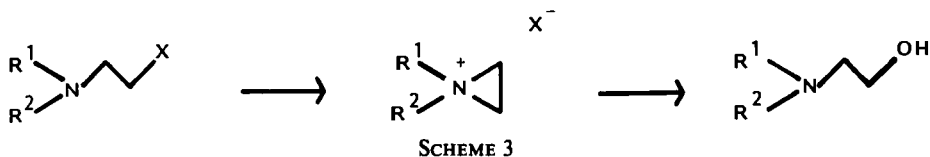
Sendaverine (**19a**)⁹ and corgoine (**19b**)¹⁰ are the only two naturally occurring 2-benzylisoquinoline alkaloids. One of their syntheses involves a key ring-opening reaction of an aziridinium salt (Scheme 3).¹¹ Thus *N*-(3-benz-

⁹ T. Kametani, K. Ohkubo, and S. Takano, *J. Pharm. Soc. Jpn.* **87**, 563 (1967); T. Kametani and K. Ohkubo, *Tetrahedron Lett.*, 4317 (1965).

¹⁰ M. U. Ibragimova, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Pri. Soedin.* **2**, 211 (1971).

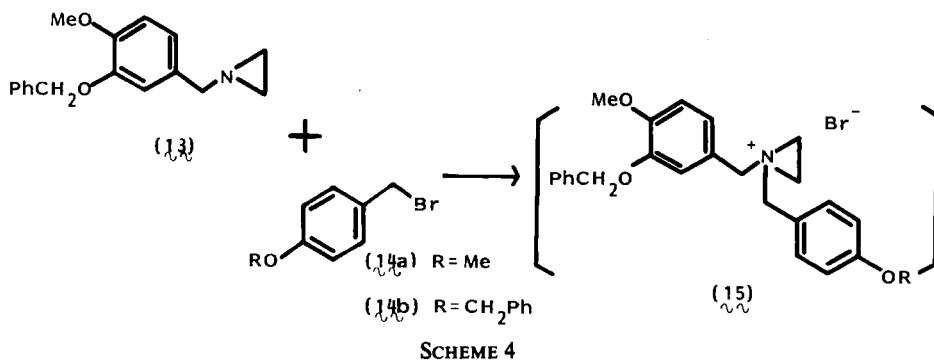
¹¹ H. Otomasu, K. Higashiyama, T. Honda, and T. Kametani, *J. C. S. Perkin I*, 2399 (1982).

loxy-4-methoxybenzyl)aziridine (**13**), prepared from 3-benzyloxy-4-methoxybenzyl chloride with ethylenimine in benzene in the presence of potassium carbonate in 96% yield, was treated with 4-methoxy- or 4-benzyloxybenzyl bromide (**14**) in refluxing acetone to furnish the ring-opened bromide **16** via the formation of the quaternary salt **15** and subsequent nucleophilic ring opening by bromide ion in quantitative yield (Scheme 4). Though Friedel–Crafts cyclization has been shown¹² to be an excellent way of constructing a tetrahydroisoquinoline nucleus, the intramolecular alkylation of the bromides **16a** and **16b** by the application of the above reaction did not give the desired products. However, the bromides **16a** and **16b** were easily converted to the alcohols **17a** and **17b** by absorption onto an alumina column and elution with benzene. It has been assumed that the conversion of the bromides to the hydroxy analogs **17a** and **17b** was facilitated by the ring-closure and ring-opening reactions of aziridines.

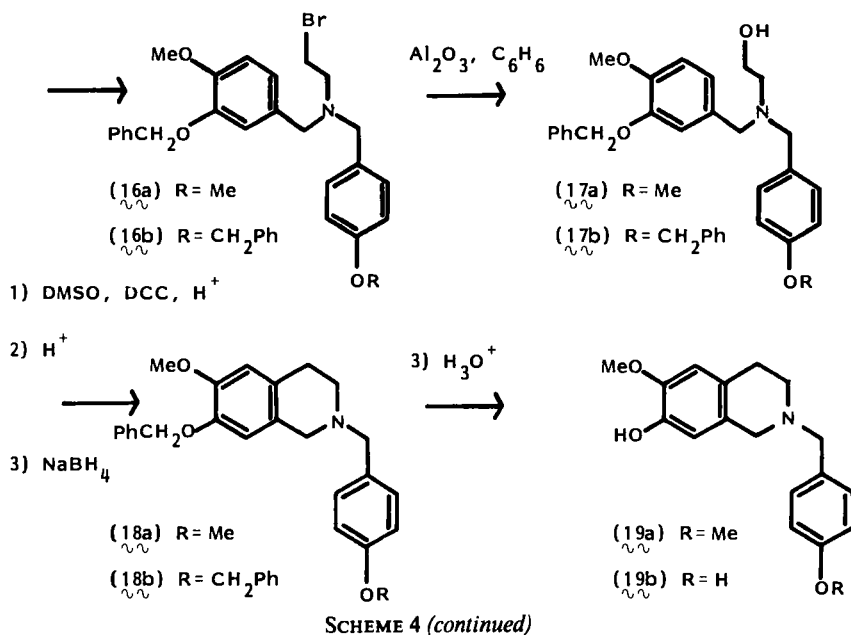


The alcohols **17a** and **17b** were further converted to the 2-benzylisoquinolines **18a** and **18b** by Moffatt oxidation and a subsequent known cyclization. Finally, debenzylation of **18a** and **18b** with hydrochloric acid afforded senvdaverine (**19a**) and corgoine (**19b**), respectively, in good yields.

This synthesis involves a ring-opening reaction of the aziridinium salts as the key step and provides a novel route to 2-alkylisoquinolines.



¹² L. W. Deady, N. Pirzada, and R. D. Topsom, *Chem. Commun.*, 799 (1971).



Moreover, this procedure should provide a useful route to construct the 1,2,3,4-tetrahydroisoquinoline nucleus in a modified Pomeranz–Fritsch-type procedure shown in Scheme 5.

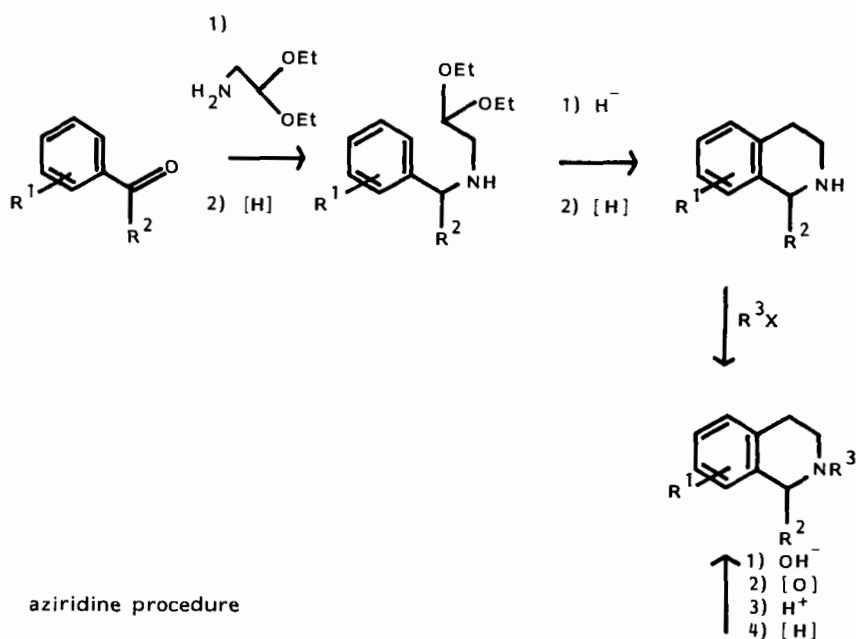
3. Reframidine

The isopavine alkaloid (±)-reframidine (**27**) was also synthesized¹³ by a ring opening reaction of a quaternary aziridinium salt as a key step (Scheme 6). The interest in the utilization of a quaternary aziridinium salt as a reactive intermediate stems not only from its high reactivity originating from the release of the strain energy inherent in a three-membered ring but also from the ease with which an ethylamine moiety can be introduced. Thus the requisite aziridine derivative **21** was prepared from deoxypiperoin (**20**)¹⁴ in three steps in 80% yield. Though the ring-opening reaction of **21** with methyl iodide gave none of the desired product, the reaction of **21** with ethyl chloro-carbonate, which could be transformed into a methyl group by reduction with lithium aluminum hydride, yielded the urethane **22** in 92% yield.

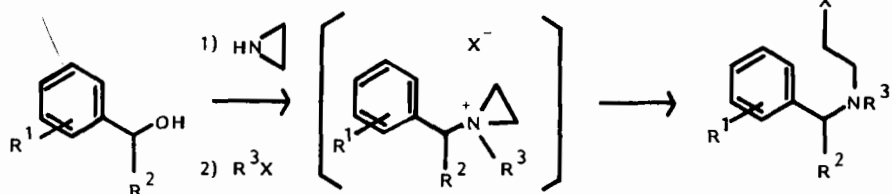
¹³ T. Kametani, K. Higashiyama, T. Honda, and H. Otomasu, *Chem. Pharm. Bull.* **32**, 1614 (1984).

¹⁴ I. Allen and J. S. Buck, *J. Am. Chem. Soc.* **52**, 310 (1930).

Pomeranz-Fritsch reaction



aziridine procedure



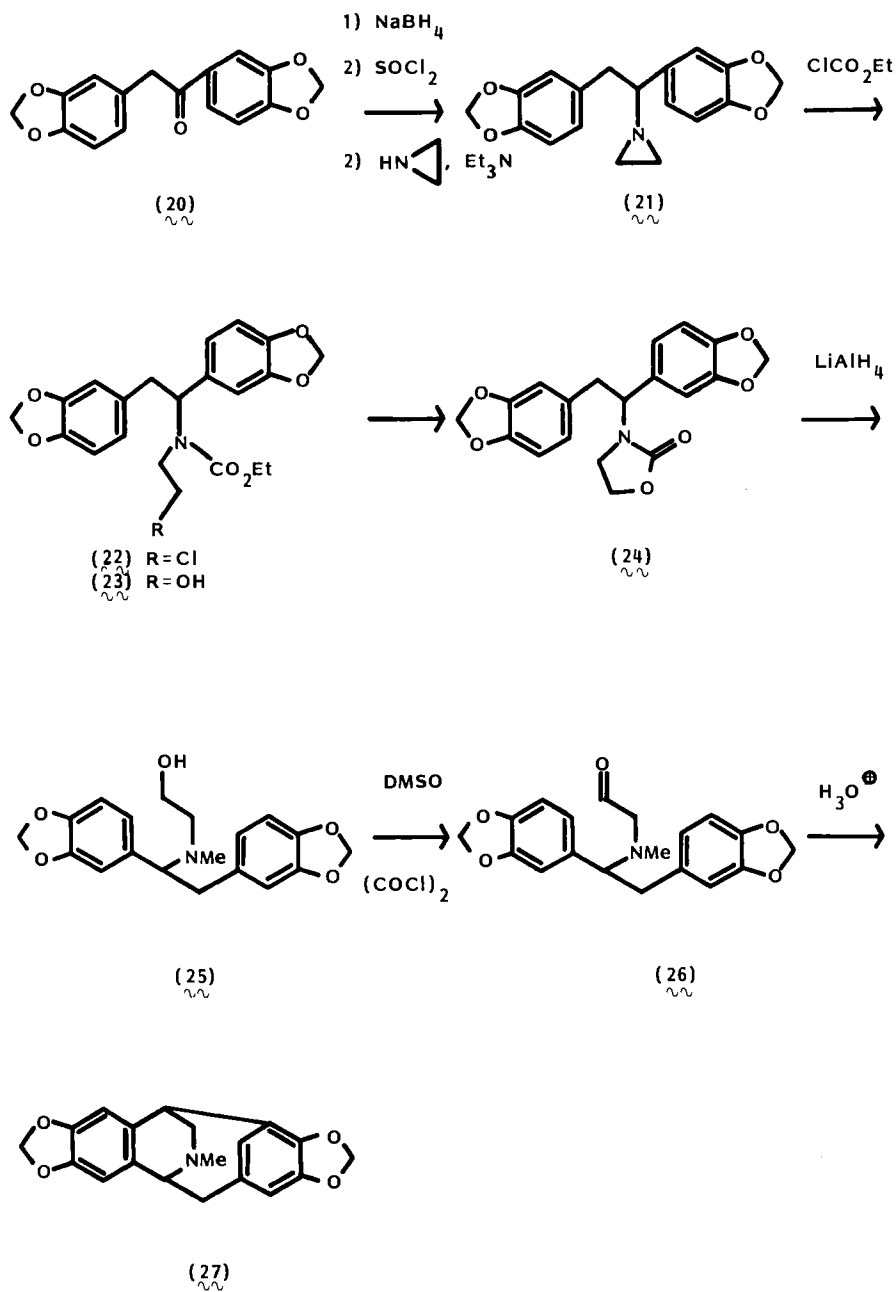
SCHEME 5

Conversion of the chloride **22** to the alcohol **23** was achieved on treatment with mercuric oxide and perchloric acid according to McKillop's procedure,¹⁵ together with the oxazolidinone **24**. The alcohol **23** was easily cyclized to the oxazolidinone **24** by passing through an alumina column, using benzene as an eluant. Reduction of **24** with lithium aluminum hydride furnished the expected alcohol **25**, whose Swern oxidation¹⁶ afforded the aldehyde **26**. The final ring closure reaction of **26**, originally developed by Battersby,¹⁷ gave (\pm)-reframidine (**27**), identical with an authentic specimen.

¹⁵ A. McKillop and M. E. Ford, *Tetrahedron* **30**, 2647 (1974).

¹⁶ A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.* **43**, 2480 (1978).

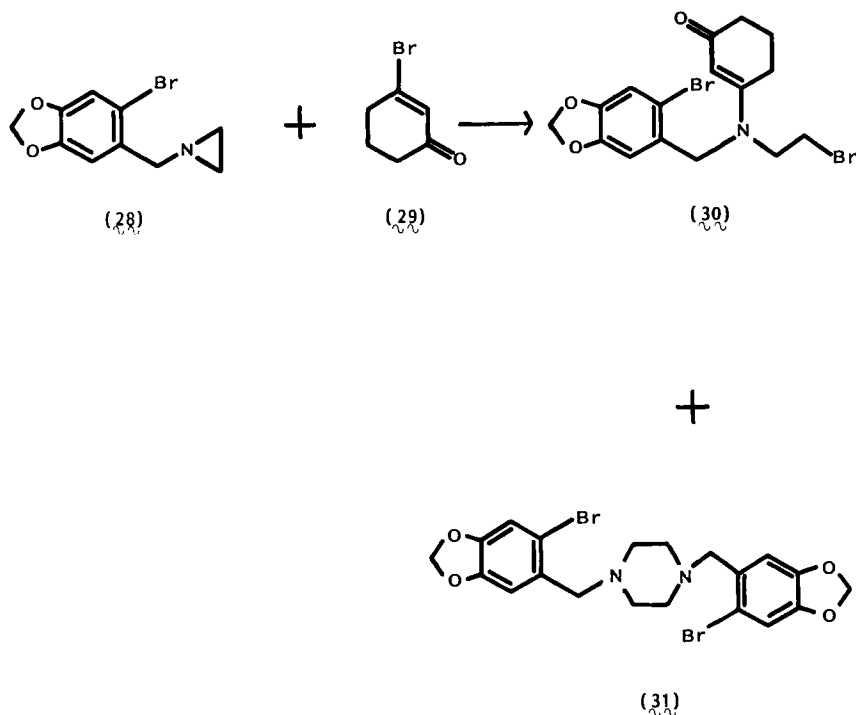
¹⁷ A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1988 (1958).



SCHEME 6

4. α -Dihydrocaranone and γ -Lycorane

Synthesis of α -dihydrocaranone (**36**) and γ -lycorane (**37**) was accomplished¹⁸ similarly to that of reframidine, employing a ring-opening reaction of an aziridinium salt formed *in situ* (Scheme 7). The known procedure^{19,20} for the synthesis of these alkaloids required the Birch reduction of an aromatic ring to prepare the starting materials. The introduction of an aromatic moiety onto the resulting amines was achieved in a later stage with some difficulty. To synthesize the tetrahydroindoline system, *N*-benzylaziridine derivative **28** was treated with 3-bromo-2-cyclohexen-1-one (**29**) in refluxing acetone to give the enaminone **30** and the piperazine **31** in 58 and 39% yields, respectively. The intramolecular γ alkylation²¹ of **30** with lithium diisopro-



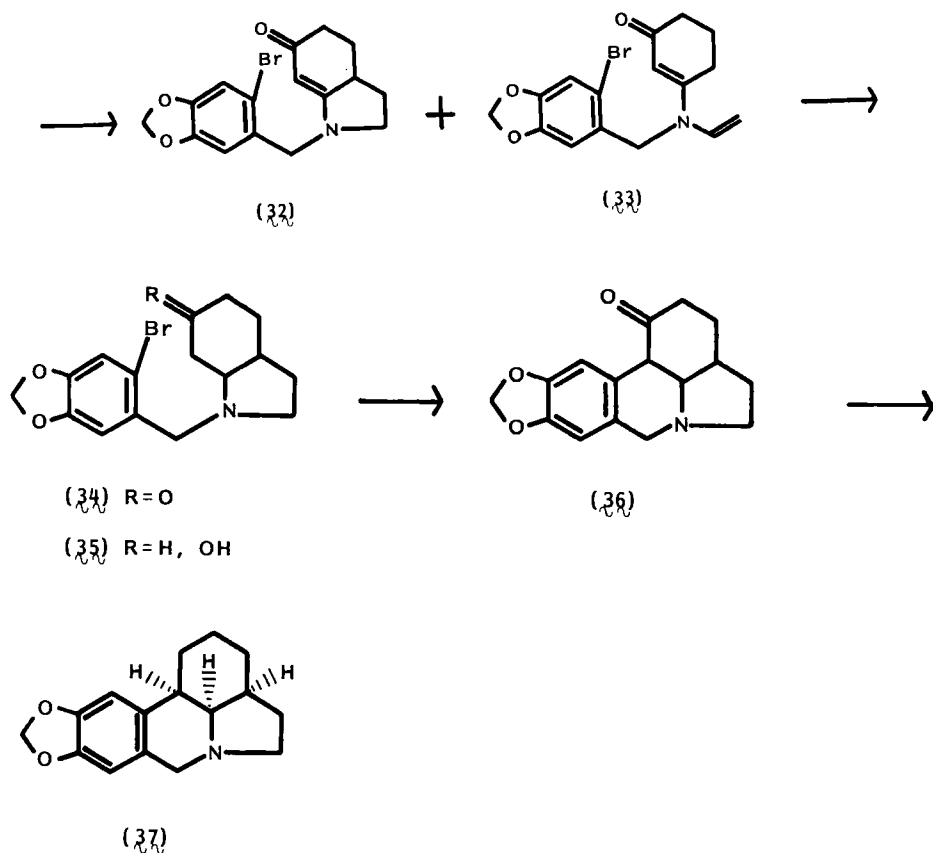
SCHEME 7

¹⁸ K. Higashiyama, T. Honda, H. Otomasu, and T. Kametani, *Planta Med.* **48**, 268 (1983).

¹⁹ N. Ueda, T. Tokuyama, and T. Sakan, *Bull. Chem. Soc. Jpn.* **39**, 2012 (1966).

²⁰ H. Iida, Y. Yuasa, and C. Kibayashi, *J. Org. Chem.* **44**, 1079 (1979); *Chem. Lett.*, 475 (1981).

²¹ T. A. Bryson and R. B. Gammill, *Tetrahedron Lett.*, 3963 (1974).

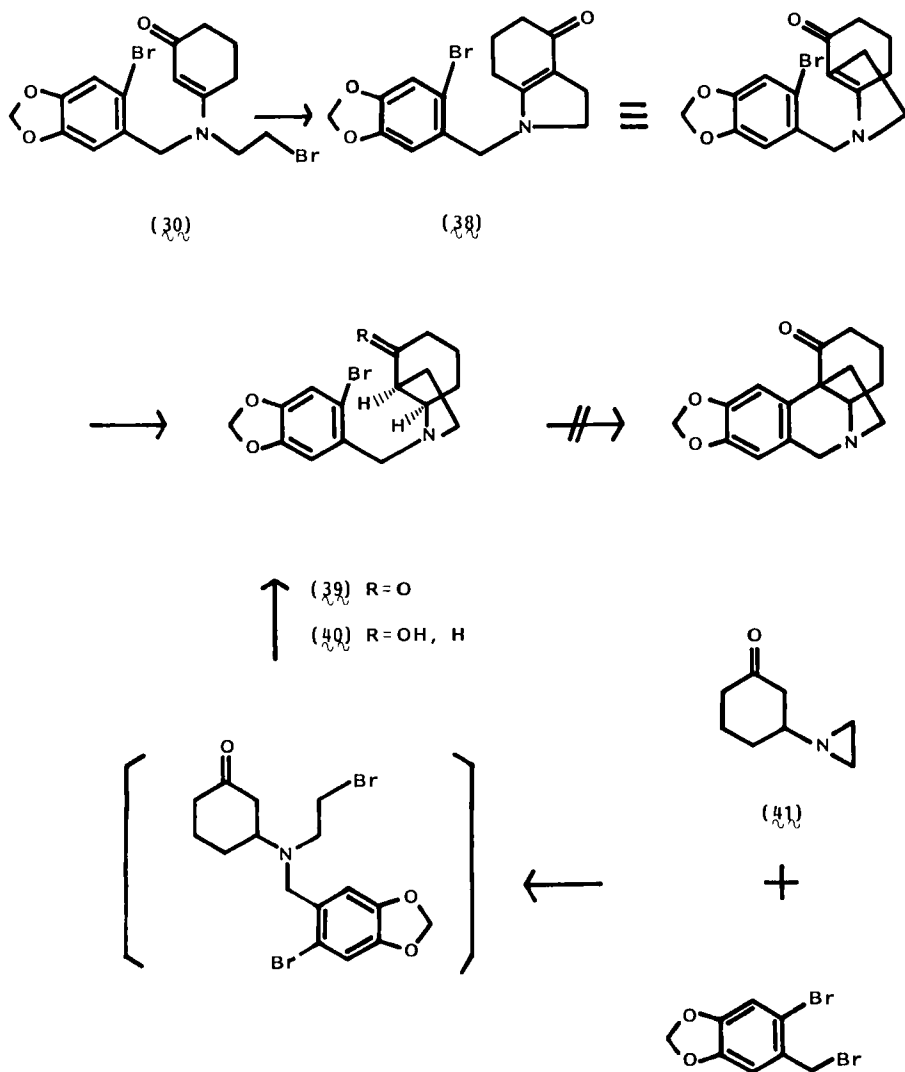


SCHEME 7 (continued)

pylamide furnished the expected indoline derivative **32** in addition to the elimination product **33**. Thus the facile synthesis of the enaminone **32** was accomplished by only two steps from the aziridine derivative **28**, employing the key ring-opening reaction of the aziridinium salt. Reduction of **32** with lithium aluminum hydride provided the ketone **34** and the alcohol **35** in 51% yield in a ratio of 3 : 7. The latter compound (**35**) was easily oxidized with the Jones reagent to the former ketone (**34**) in 75% yield. Since both compounds **32** and **34** have already been converted to α -dihydrocaranone (**36**) and γ -lycorane (**37**) by Iida and also by Sakan this constitutes a formal synthesis of these alkaloids.

Interestingly, the bromoenaminone **30** was converted to the α -alkylation product **38** by heating it in the presence of sodium iodide in 75% yield (Scheme 8). Again, lithium aluminum hydride reduction gave the ketone **39**

together with the alcohol **40**. Conversion of the latter to the former was easily achieved by Jones oxidation. The ketone **39** was also derived from the reaction of the aziridine **41** with 6-bromo-3,4-methylenedioxybenzyl bromide in one step. However, various attempts at the cyclization of **39** into a crinane-type alkaloid were unsuccessful.



SCHEME 8

5. Erythrinan Alkaloid

Further application of the ring-opening reaction of an aziridinium salt as a key step in the synthesis of isoquinoline alkaloids by Kametani leads to the investigation of the construction of an erythrinan skeleton (Scheme 9).²² Treatment of the *N*-phenethylaziridine **42**, prepared (87%) from 3,4-dimethoxyphenethyl bromide and ethylenimine, with 3-bromo-2-cyclohexen-1-one in refluxing acetone furnished the bromoenaminone **43** and the dimer **44** in 55 and 44% yields, respectively. Intramolecular γ alkylation of **43** with lithium diisopropylamide afforded the enaminone **45**, which was already converted²³ to hexahydroapoerysopine dimethyl ether (**46**) arising from the acid-catalyzed apo rearrangement of tetrahydroerythraline. The thermal cyclization of **43** in the presence of sodium iodide brought about the α cyclization site-selectively to afford the enaminone **47** (82%). Reduction of **47** with lithium aluminum hydride gave rise to the alcohol **49** (73%), together with the ketone **48** and the cis alcohol **50** in 2 and 15% yields, respectively. Mercuric acetate-mediated cyclization of **49** gave the isoquinoline derivative **51** together with the dehydrated product **52** instead of the expected erythrinan-type compound. Although the yield was not satisfactory for further investigation, the enaminone **47** was converted to the desired compound **53** on treatment with phosphoric acid. The stereochemistry of **53** was determined by comparison with an authentic sample prepared from the known compound **56** by successive ketalization (**55**), reduction, and deketalization.

B. UTILIZING DIAZO COMPOUNDS

1. Reframidine

Intermolecular diazomethane-iminium insertion followed by a ring-expansion reaction was originally reported by Leonard and Jann.²⁴ Pfeifer and co-workers²⁵ also observed that this reaction could be applied to hydrastinine (**57**) and cotarnine (**58**) to give the ring-expanded azepine derivatives **59** and **60**, respectively (Scheme 10). Bernhard and Snieckus²⁶ showed that the aziridinium perchlorate **61** was an intermediate in the above reaction with hydrastinine perchlorate.

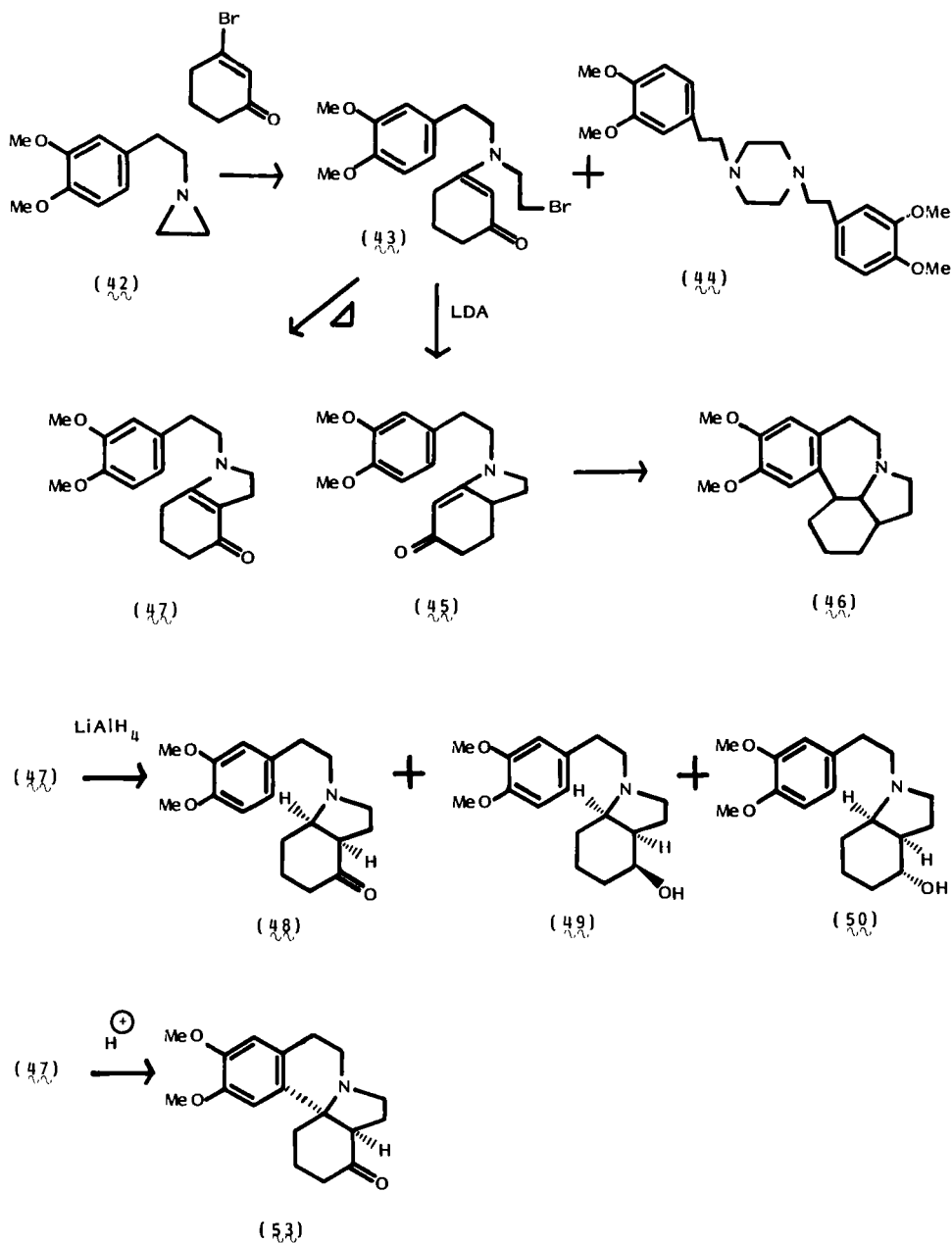
²² T. Kametani, K. Higashiyama, T. Honda, and H. Otomasu, *Heterocycles* **22**, 569 (1984).

²³ H. Iida, T. Takarai, and C. Kibayashi, *J. Org. Chem.* **43**, 975 (1978).

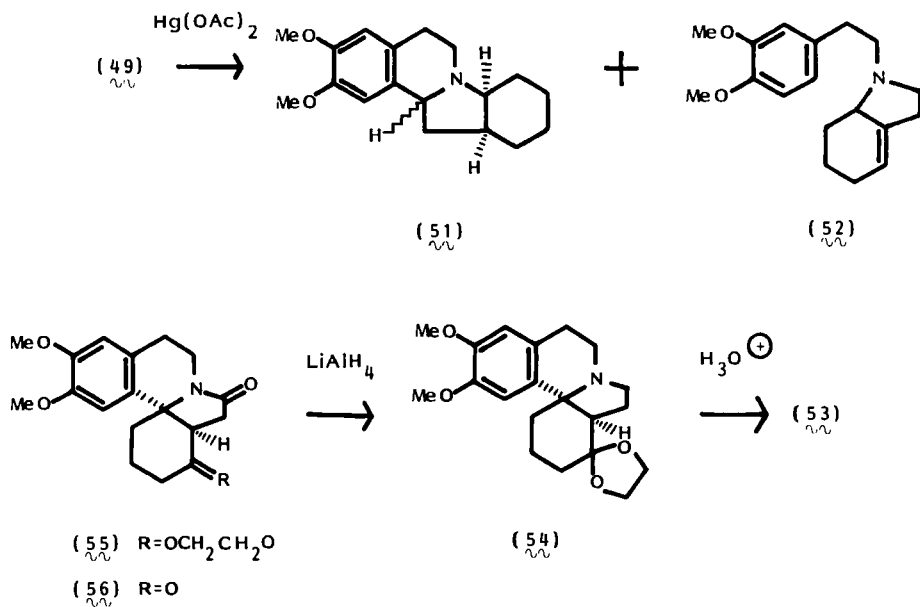
²⁴ N. J. Leonard and K. Jann, *J. Am. Chem. Soc.* **84**, 4806 (1962).

²⁵ B. Goerber, S. Pfeifer, V. Hanuš, and G. Engelhardt, *Arch. Pharm. (Weinheim, Ger.)* **301**, 763 (1968).

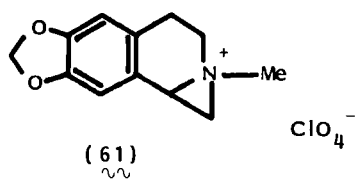
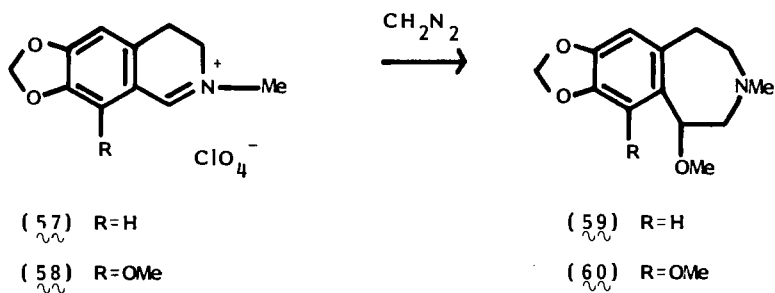
²⁶ H. O. Bernhard and V. Snieckus, *Tetrahedron* **27**, 2091 (1971).



SCHEME 9

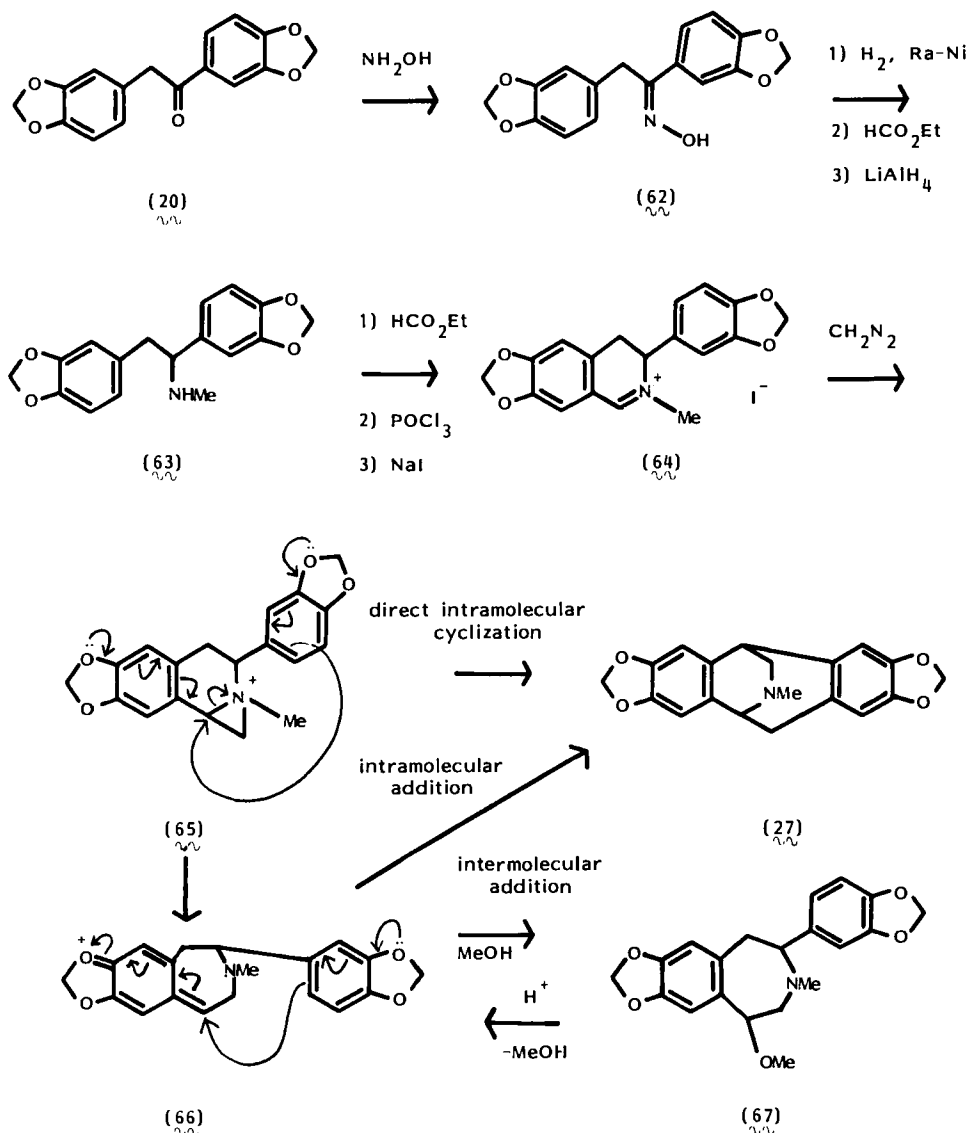


SCHEME 9 (continued)



SCHEME 10

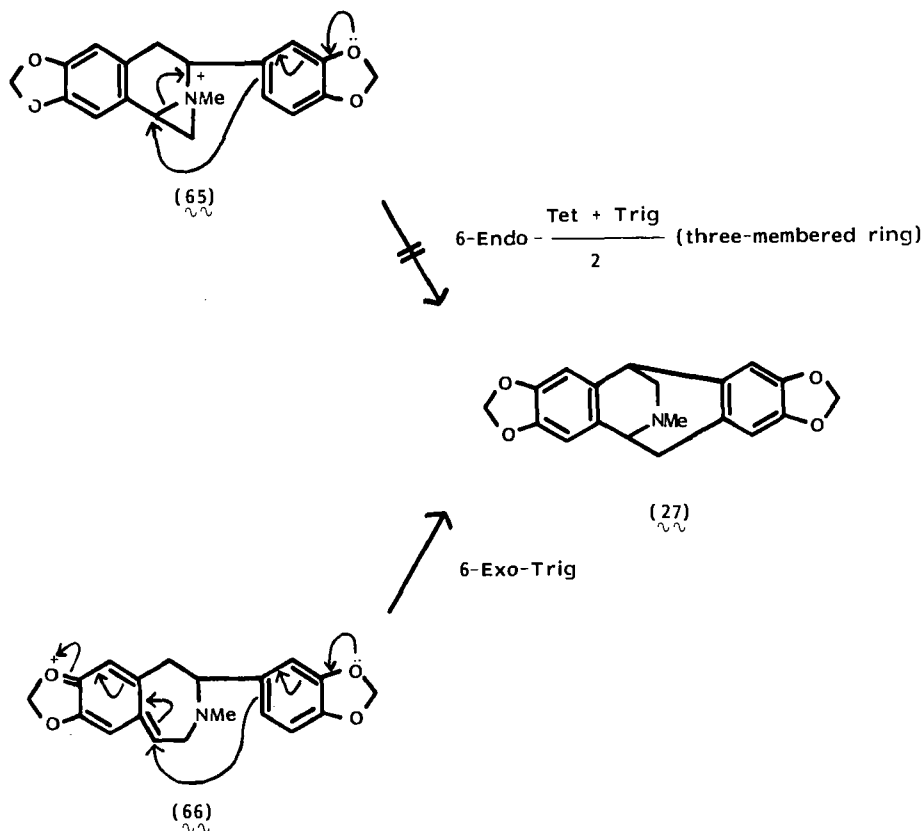
Based on a consideration of the above results, it is reasonable to assume that the reaction of a 3-(alkoxyphenyl)isoquinolinium iodide with diazomethane would give an aziridinium salt, which might then be transformed into an isopavine via a one-step ring expansion and ring closure involving intramolecular attack by the electron-rich alkoxyphenyl group.



SCHEME 11

Thus the 3-substituted isoquinolinium iodide **64**, prepared from deoxyepiperoin **20** via the oxime **62** and the amine **63** as outlined in Scheme 11, was treated with an excess of ethereal diazomethane. When the resulting crude aziridinium iodide **65** in 6 *N* hydrochloric acid was kept at room temperature for 1 week, (\pm)-reframidine (**27**) was isolated in 20% yield. Reframidine was also formed, in 35% yield, when the 3-benzazepine **67**, obtained in 20% yield by refluxing the crude aziridinium iodide **65** with 1% methanolic hydrogen chloride, was treated with 6 *N* hydrochloric acid at ambient temperature for 1 week.

Although there was no evidence for the formation of the azepine **67**, the ready conversion to the isopavine **27** suggested that this reaction did not involve an intramolecular cyclization of the aziridinium salt **65** effected by the 3-(alkoxyphenyl) group, but the 6-oxygen atom on the isoquinoline ring was involved in forming a transient quinonoid intermediate (**66**), which was

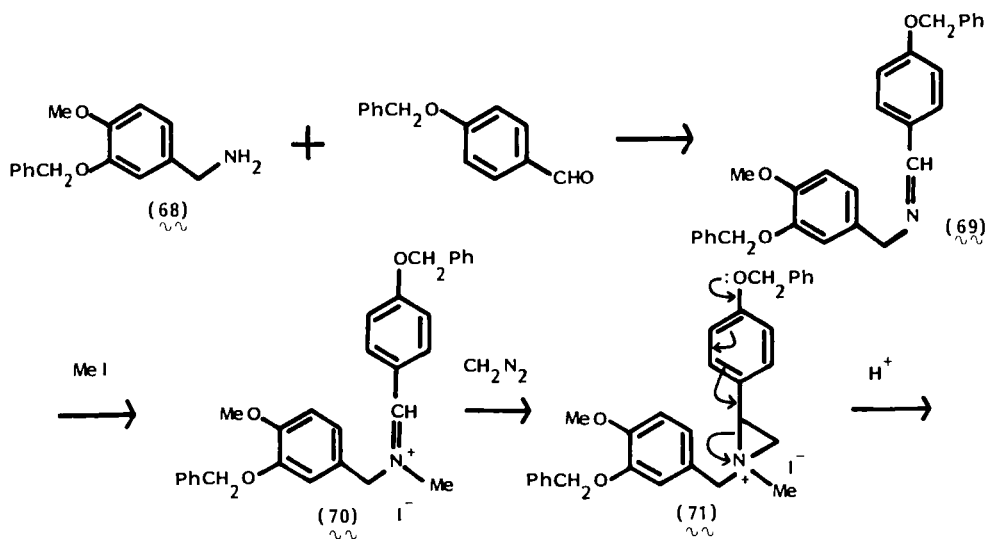


SCHEME 12

then attacked either intramolecularly by the 3-(alkoxyphenyl) group or intermolecularly by a methoxy group, depending on the reaction conditions.²⁷ These assumptions are in accord with Baldwin's rule²⁸ shown in Scheme 12.

2. Cherylline

The 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid (\pm)-cherylline (**74**) has also been synthesized²⁹ by a ring opening of the quaternary aziridinium salt, followed by a cyclization of the quinone methide, generated *in situ* (Scheme 13). The aziridinium salt **71** was synthesized as follows. Condensation of 3-benzyloxy-4-methoxybenzylamine (**68**) with 4-benzyloxybenzaldehyde in refluxing benzene gave rise to the Schiff base **69**, which was then treated with an excess of methyl iodide to furnish the quaternary salt **70**. Further treatment of **70** with an excess of ethereal diazomethane and subsequently 1% methanolic hydrochloric acid yielded di-*O*-benzylcherylline (**73**), presumably via the aziridinium salt **71** and the quinone methide **72**, in 53% yield from **69**. Since the direct intramolecular cyclization of **71** to **73** is not allowed according to Baldwin's rule, it is reasonable to assume the formation of the quinone methide **72** as a transient compound. Finally, di-*O*-benzylcheryl-

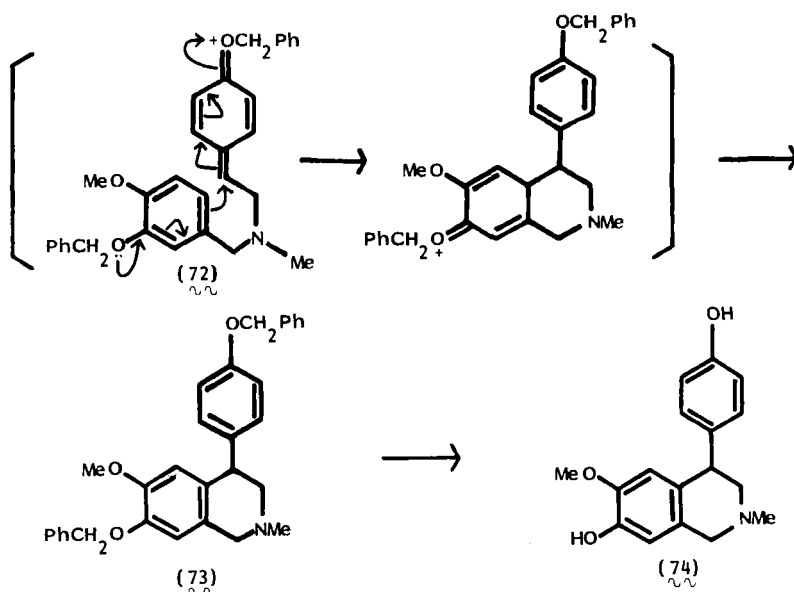


SCHEME 13

²⁷ T. Kametani, S. Hirata, and K. Ogasawara, *J. C. S. Perkin I*, 1466 (1973).

²⁸ J. E. Baldwin, *Chem. Commun.*, 734, 736 (1976).

²⁹ T. Kametani, K. Higashiyama, T. Honda, and H. Otomasu, *J. C. S. Perkin I*, 2935 (1982).



SCHEME 13 (continued)

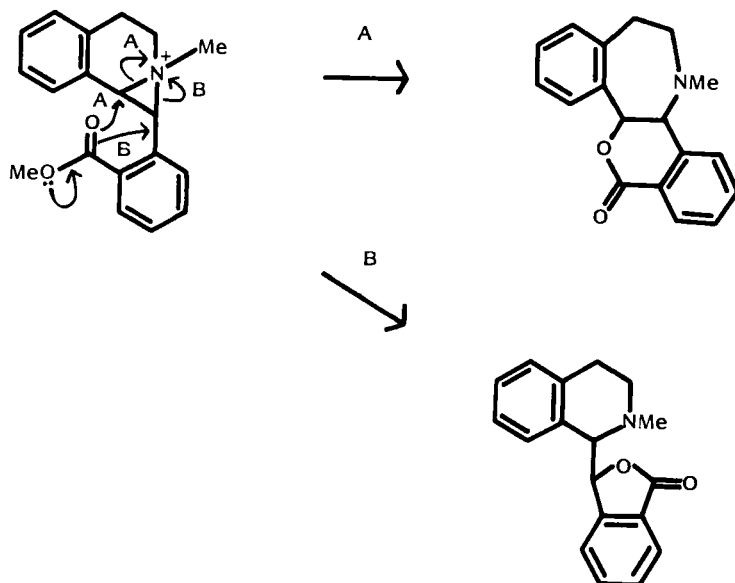
line (73) was hydrolyzed with 10% ethanolic hydrochloric acid to give (±)-cherylline (74).

3. Cordrastine and Hydrastine

Synthesis of the phthalidylisoquinoline alkaloids cordrastine (82) and hydrastine (83) has been achieved³⁰ by application of an aziridinium ring opening. A 2-methyl-3,4-dihydroisoquinolinium iodide was treated with 2-diazomethylbenzoate, in the hope of obtaining the rheadan or the phthalidylisoquinoline, as shown in Scheme 14.

Intramolecular nucleophilic attack of the carboxylate group on the aziridinium system could take place by routes A and B, leading to rheadan or phthalidylisoquinoline. The requisite diazomethylbenzoate 79 was synthesized as follows (Scheme 15). Methyl 6-bromo-2,3-dimethoxybenzoate (75), prepared from 2-hydroxy-3-methoxybenzaldehyde in six steps, with copper(I) cyanide gives the cyanide 76 (85%); then hydrogenation over Raney nickel in ethanol at 80°C under 80 atm of hydrogen afforded 5,6-dimethoxyphthalimidine (77). N-Nitrosation of 77 with sodium nitrite in concentrated hydrochloric acid at ambient temperature gave the N-nitrosophthali-

³⁰ T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *J. C. S. Perkin I*, 1221 (1976).



SCHEME 14

midine **78**, whose treatment with 5 *N* sodium methoxide in methanol according to Oppé's procedure³¹ furnished the desired diazomethylbenzoate **79**. An ethereal solution of the diazo compound **79** was then treated with 3,4-dihydro-6,7-dimethoxy-2-methyl- (**80**) and 3,4-dihydro-6,7-methylenedioxy-2-methylisoquinolinium salts (**81**) at ambient temperature for 2 days to afford cordrastine (**82**) and hydrastine (**83**) in 10–15% yields, respectively. No rheadan-type intermediate was detected.

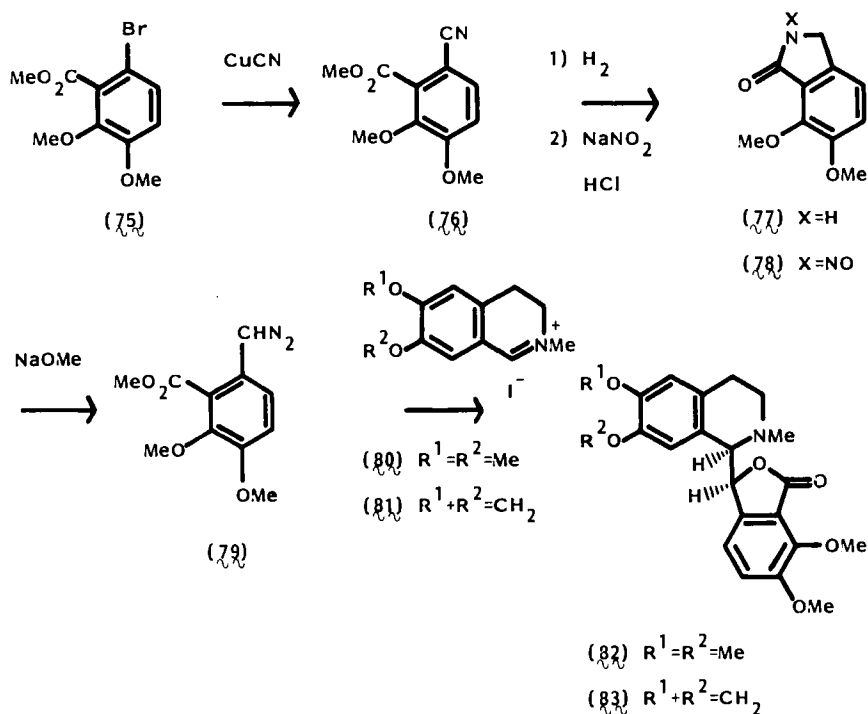
Although the formation of phthalidylisoquinolines presumably proceeds via the aziridinium salt by route B in Scheme 14, the mechanism shown in Scheme 16 is also a possibility.

4. Morphinan Alkaloids

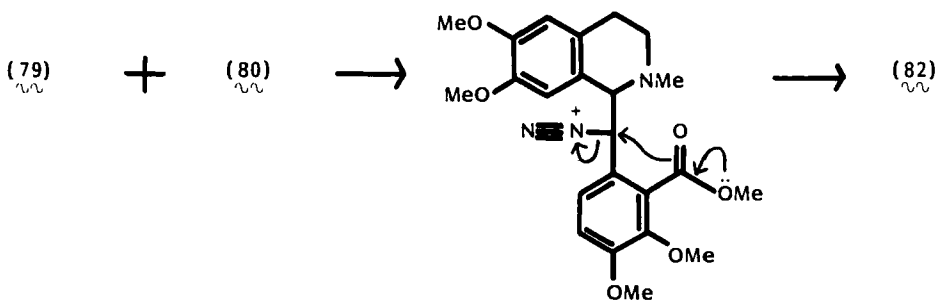
A diazomethane–iminium insertion reaction was utilized during the formation of a methylene bridge in the synthesis of a morphinan-type compound from a corresponding octahydroisoquinoline (Scheme 17).³² The requisite octahydroisoquinoline (**85**) was prepared from the tetrahydropyri-

³¹ A. Oppé, *Ber. Dtsch. Chem. Ges.* **46**, 1095 (1913).

³² D. A. Evans, C. H. Mitch, R. C. Thomas, D. M. Zimmerman, and R. L. Robey, *J. Am. Chem. Soc.* **102**, 5956 (1980).



SCHEME 15

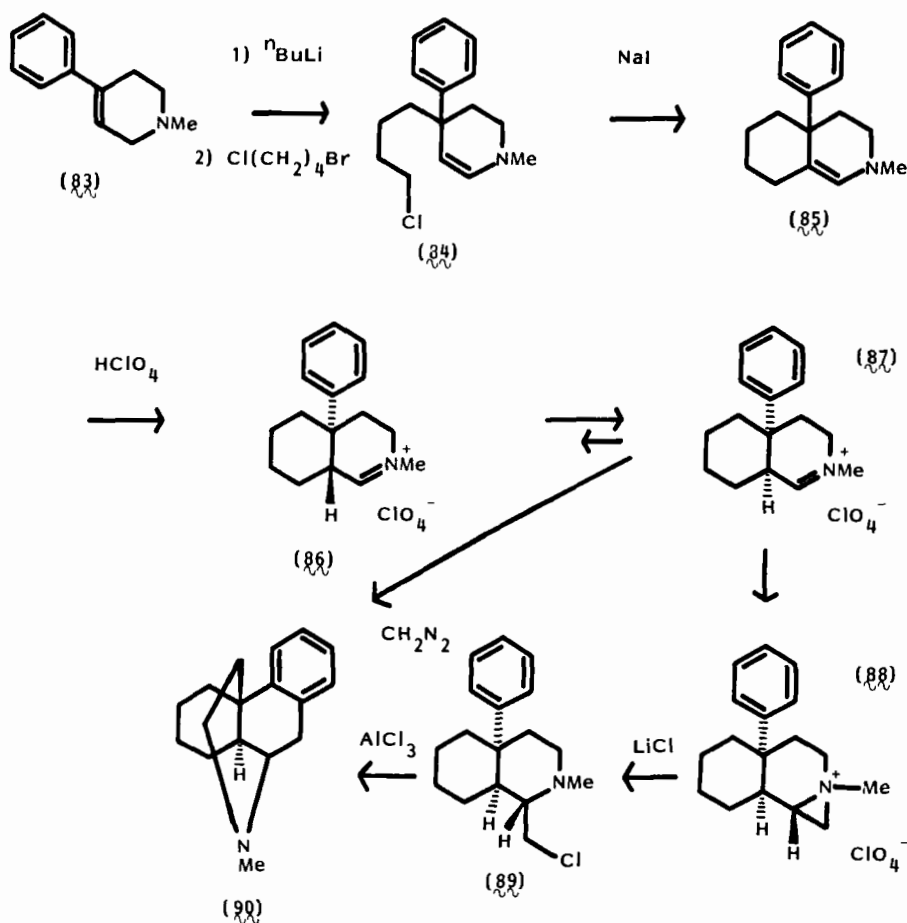


SCHEME 16

dine 83, employing an enamine metalation-alkylation reaction³³ as a key step via the chloride 84. Treatment of 85 with ethereal perchloric acid, followed by solvent removal, gave the kinetically generated trans-fused perchlorate 86, which was easily isomerized to the thermodynamic cis-fused salt 87. Addition of diazomethane to the salt 87 afforded the desired aziri-

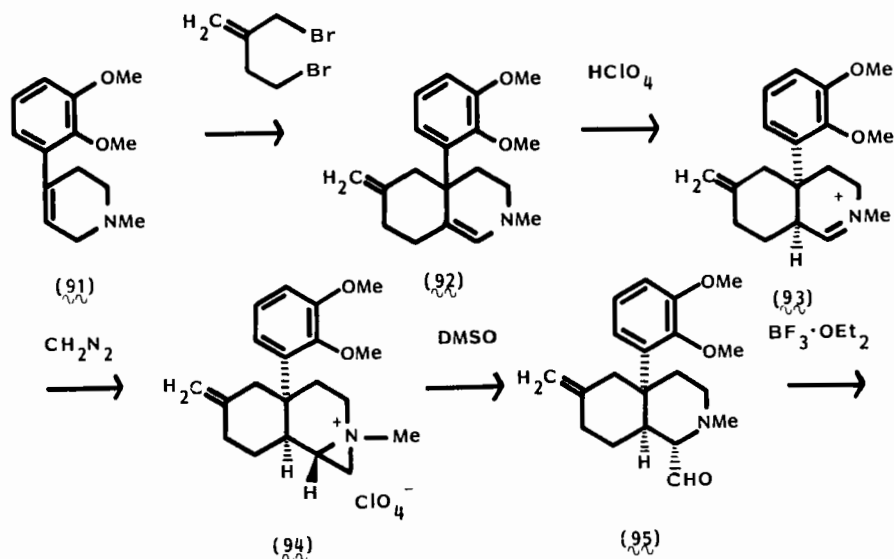
³³ R. Levine and V. Rell, U.S. Patent 3,824,242 (1974); S. F. Martin and M. F. Dupriest, *Tetrahedron Lett.*, 3925 (1977).

dinium perchlorate **88** as a crystalline form stereoselectively. The high degree of stereoselection in this addition process was rationalized by assuming that the addition of a nucleophile occurred from the convex face of the bicyclic ring system. Regiospecific cleavage of the highly labile aziridinium ring with lithium chloride gave rise to the chloride **89** whose intramolecular Friedel-Crafts reaction with AlCl_3 brought about the ring-closure reaction to form *N*-methyl-14 α -morphinan (**90**). It is worth noting that careful scrutiny of the reaction of the salt **87** with diazomethane revealed that a 15% yield (30% in acetone) of the morphinan **90** was formed directly in competition with aziridinium ion formation.



SCHEME 17

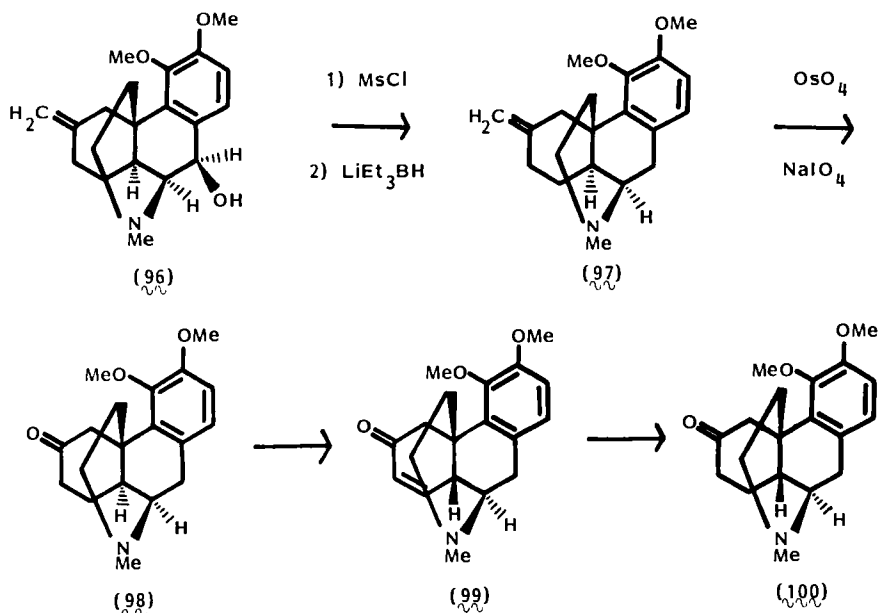
A formal total synthesis of (\pm)-morphine has been achieved by adopting the above synthetic route (Scheme 18).³⁴ The tetrahydropyridine **91**, prepared from the reaction of *N*-methyl-4-piperidone with 2,3-dimethoxyphenyllithium, followed by dehydration, was converted to the bicyclic enamine **92** by treatment with the allylic dibromide. Kinetic protonation of **92** with perchloric acid gave the trans-fused immonium salt, which upon dissolution in methanol equilibrated to the thermodynamically preferred cis isomer **93**. Treatment of **93** with diazomethane brought about the formation of the aziridinium salt **94**, which was readily transformed into the α -amino aldehyde **95** by its oxidation with dimethyl sulfoxide. It is also worth noting that the "Kornblum oxidation" of aziridinium salts leads to the construction of α -amino aldehydes efficiently. Lewis-acid-catalyzed cyclization of **95** afforded the morphinan carbinol **96** in 80% yield. Successive mesylation and reduction of the mesylate derived from **96** with LiBEt_3H afforded morphinan (**97**) in excellent yield. In this instance, direct conversion of **93** to **97** by treatment with diazomethane gave approximately 1% of the desired product. Lemieux-Johnson oxidation of **97** under acidic conditions furnished the ketone **98**, which was previously transformed into (\pm)-morphine by Gates.³⁵ In order to confirm the structure of **98**, its conversion to the known



SCHEME 18

³⁴ D. A. Evans and C. H. Mitch, *Tetrahedron Lett.* **23**, 285 (1982).

³⁵ M. Gates and G. Tschudi, *J. Am. Chem. Soc.* **78**, 1380 (1956).



SCHEME 18 (continued)

C-14 epimer **100** via base-catalyzed equilibration and subsequent reduction of the α,β -unsaturated ketone **9** was also carried out. Thus the formal total synthesis of (\pm)-morphine has been accomplished by employing the oxidation of the aziridinium salt as a key step.

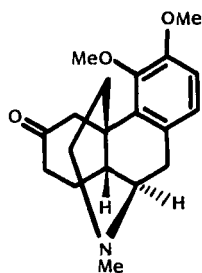
A total synthesis of (\pm)-codeine also utilized the aziridinium salt **94** as a key intermediate,³⁶ which was converted to **100** via epidihydrothebainone methyl ether (**98**) according to Evans's procedure. Specific ether cleavage reaction of **100** with NaSEt afforded dihydrothebainone (**101**) in 100% yield. Since dihydrothebainone (**101**) had already been transformed³⁷ into codeine (**102**), this synthesis constitutes a formal synthesis of **102** (Scheme 19).

A later report³⁸ of the total synthesis of *O*-methylpallidine (**106**) involved construction of the morphinan nucleus by addition of diazomethane to an iminium salt. The requisite iminium salt **104** was synthesized from the ketone **103** as shown in Scheme 20. When the iminium salt **104** was treated with diazomethane, the morphinan **105** was directly formed in 30% yield along with the aziridinium ion. In Evans's morphine synthesis, a morphinan product was produced directly in 30% yield from reaction of diazomethane

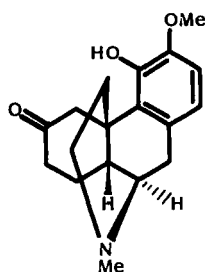
³⁶ W. H. Moos, R. D. Gless, and H. Rapoport, *J. Org. Chem.* **48**, 227 (1983).

³⁷ D. D. Weller and H. Rapoport, *J. Med. Chem.* **19**, 1171 (1976).

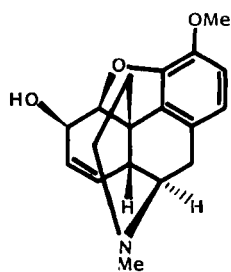
³⁸ J. E. McMurry and V. Farina, *Tetrahedron Lett.* **24**, 4653 (1983); J. E. McMurry, V. Farina, W. J. Scott, A. H. Davidson, D. R. Summers, and A. Shenvi, *J. Org. Chem.* **49**, 3803 (1984).



(100)

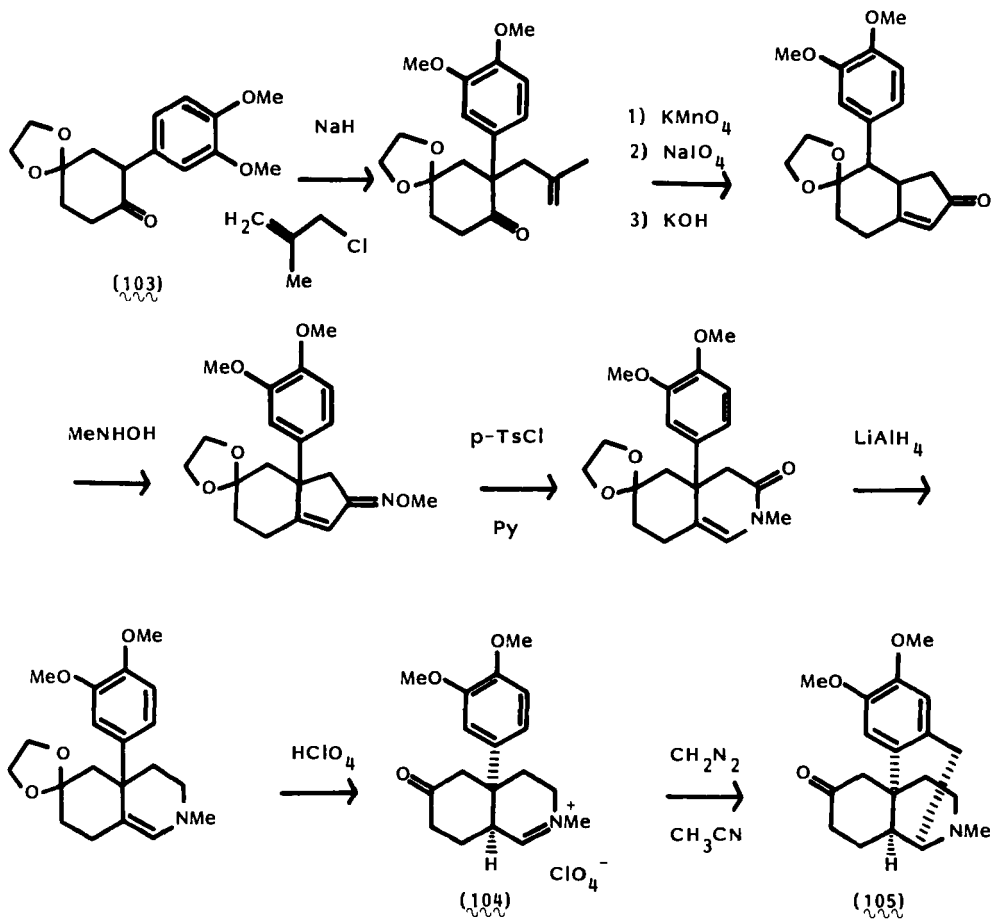


(101)

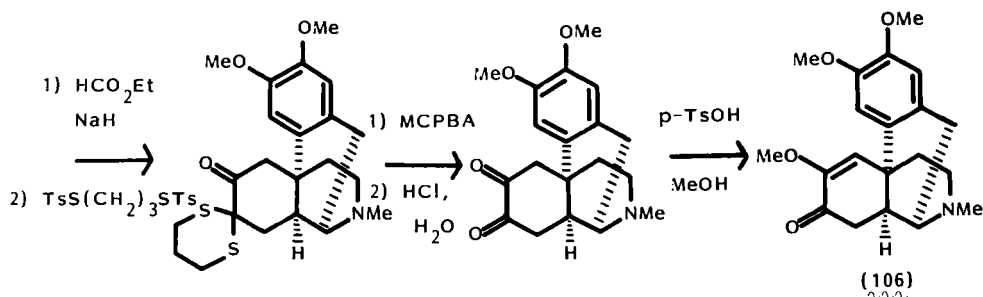


(102)

SCHEME 19



SCHEME 20



SCHEME 20 (continued)

with the iminium salt, which contains an unsubstituted aromatic ring, whereas the treatment of the iminium salt bearing a more nucleophilic dimethoxyphenyl group with diazomethane afforded only 1% of the desired morphinan product. These results suggested that the oxygen lone-pair electrons of the C-4 methoxyl group interfere with the desired cyclization by reacting with the intermediate diazonium ion produced by addition of diazomethane. Ketone **105** was further converted to *O*-methylpallidine (**106**) by several steps.

C. OTHERS

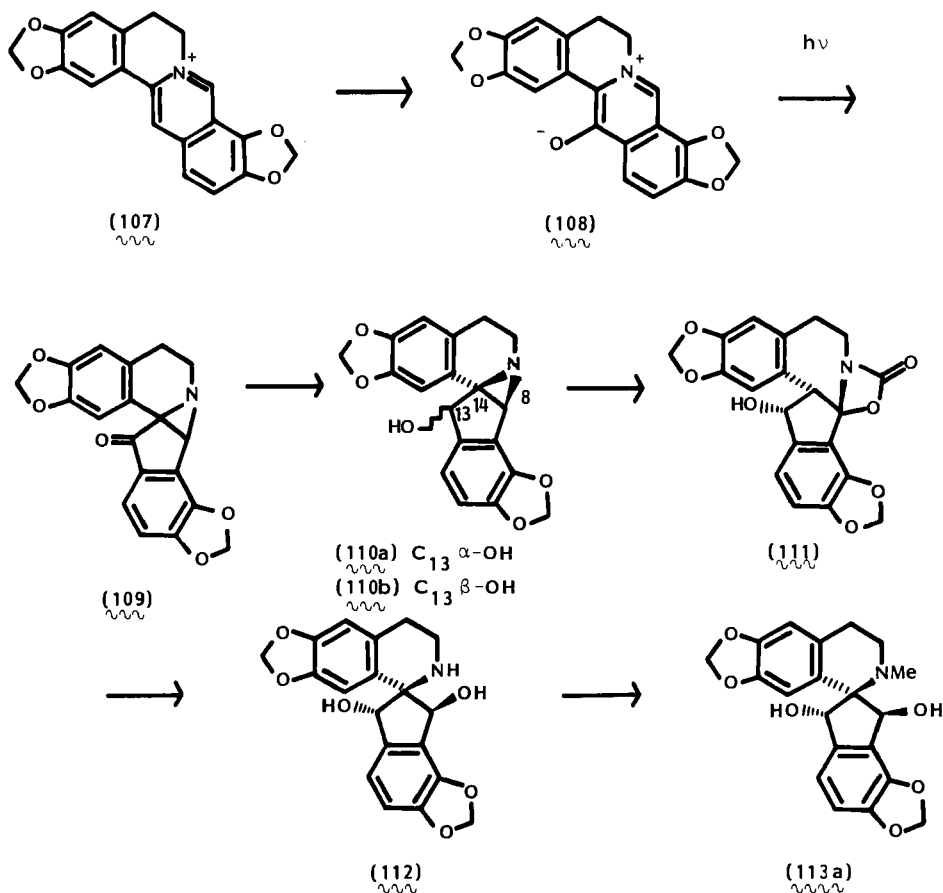
1. Ochrobirine and Fumaricine (Ochotencine Alkaloids)

A spirobenzylisoquinoline alkaloid, ochrobirine (**113a**), has been synthesized from its biogenetic precursor, coptisine (**107**) (Scheme 21). The key reaction presented in this biomimetic and stereoselective conversion involves a regioselective C-8—N bond fission of the aziridine **109**, which is formed from the betaine **108** by photochemical valence tautomerization.³⁹ Thus the irradiation of coptisinephenolbetaine⁴⁰ (**108**) with a high-pressure mercury lamp equipped with a pyrex filter afforded the aziridine **109** in 63% yield; subsequent reduction with lithium tri-*tert*-butoxyaluminum hydride furnished two diastereomeric alcohols [**110a** (64%) and **110b** (20%)]. The major alcohol (**110a**) was further converted to the oxazolidinone **111** by refluxing with ethyl chloroformate. Alkaline hydrolysis of **111** by refluxing with 30% aqueous potassium hydroxide in dioxane gave the amino diol **112**.

³⁹ M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Lett.*, 3749 (1979).

⁴⁰ P. W. Jeffs and J. D. Scharver, *J. Org. Chem.* **40**, 644 (1975).

Finally, the N-methylation of **112** with methyl iodide in tetrahydrofuran led to the formation of (±)-ochrobirine (**113a**).⁴¹



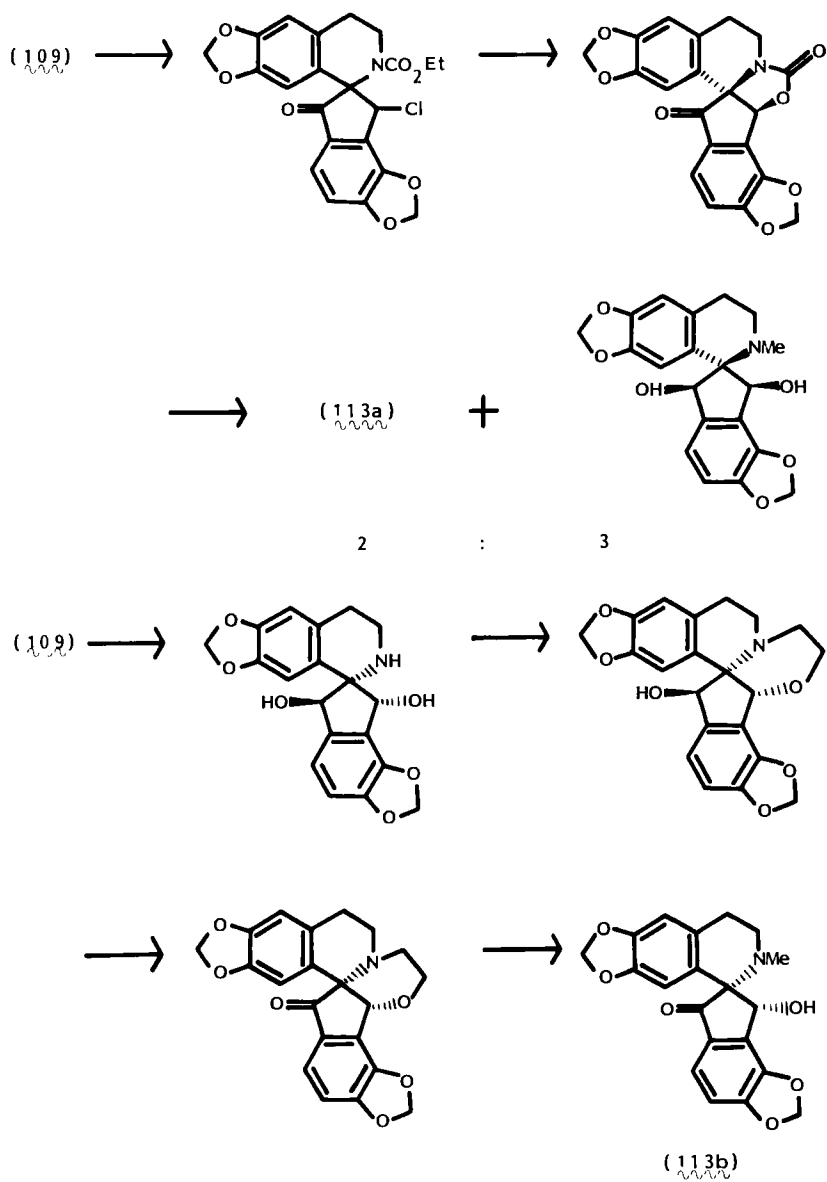
SCHEME 21

Alternatively, (±)-ochrobirine (**113a**) was synthesized from the aziridine **109** via a different route, as shown in Scheme 22, but the last step was found to be nonstereoselective. (±)-Corydaine (**113b**) was also synthesized from **109** by the application of the same method.^{41a}

A novel synthesis of (±)-fumaricine (**116**) from the dehydroberbine (**114**)

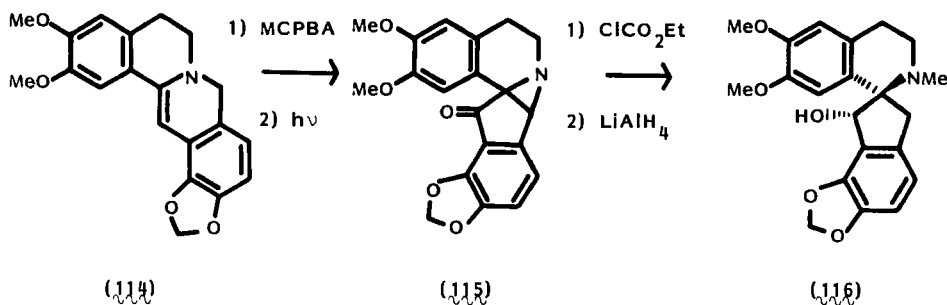
⁴¹ M. Hanaoka, S. Sakurai, T. Ohshima, S. Yasuda, and C. Mukai, *Chem. Pharm. Bull.* **30**, 3446 (1982).

^{41a} M. Hanaoka, A. Ashimori, and S. Yasuda, *Heterocycles* **22**, 2263 (1984).



SCHEME 22

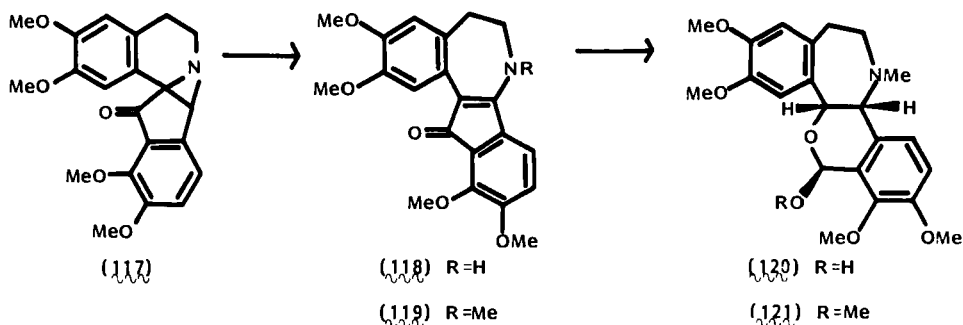
was also achieved by a similar strategy, which involves the aziridine derivative **115** as a key intermediate (Scheme 23).⁴²



SCHEME 23

2. (\pm)-*cis*-Alpinigenine, (\pm)-*cis*-Alpinine, and (\pm)-Fumaritrine (Rheadan Alkaloids)

The aziridine derivative **117**, a photochemical valence tautomerization product of berberinephenolbetaine, was also converted into the benzindanoazepines by regioselective C-14—N bond cleavage (Scheme 24).⁴³ The treatment of **117** with *p*-toluenesulfonic acid in benzene under reflux gave rise to the benzindenoazepine **118** whose N-methylation with dimethyl sulfate in HMPA in the presence of sodium hydride afforded the *n*-methyl derivative **119**.⁴⁴ Since **119** has already been converted⁴⁵ to (\pm)-*cis*-alpinigenine (**120**) and (\pm)-*cis*-alpinine (**121**), this synthesis constitutes a formal synthesis of these alkaloids.



SCHEME 24

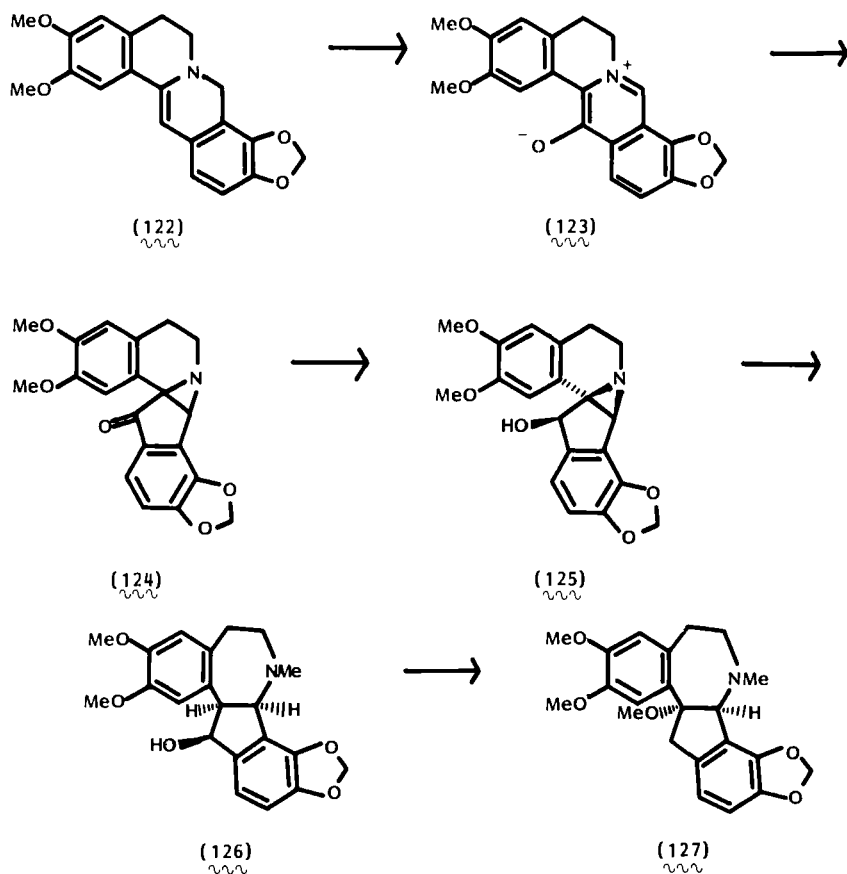
⁴² M. Hanaoka, S. Yasuda, Y. Hirai, K. Nagami, and T. Imanishi, *Heterocycles* **14**, 1455 (1980).

⁴³ M. Hanaoka, M. Inoue, K. Nagami, Y. Shimada, and S. Yasuda, *Heterocycles* **19**, 313 (1982).

⁴⁴ M. Hanaoka, M. Inoue, S. Sakurai, Y. Shimada, and S. Yasuda, *Chem. Pharm. Bull.* **30**, 1110 (1982).

⁴⁵ K. Orito, R. H. Manske, and R. Rodorigo, *J. Am. Chem. Soc.* **96**, 1944 (1974).

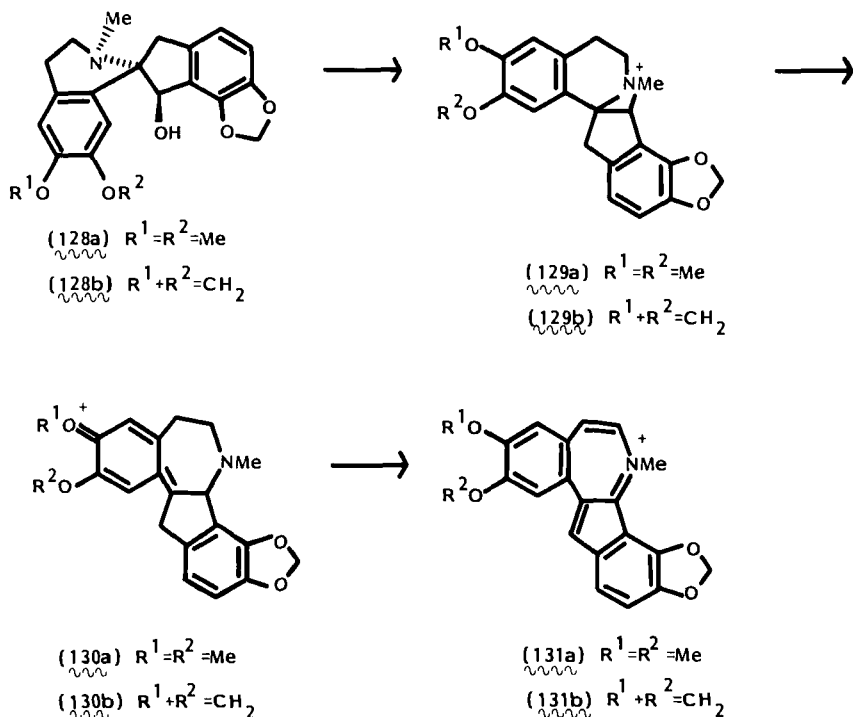
The similar conversion of dihydroepiberberine (**122**) to (\pm)-fumaritrine (**127**) was achieved by the same author (Scheme 25). Epiberberinephenol-betaine (**123**), derived from **122** by oxidation with *m*-chloroperbenzoic acid, was irradiated in methanol with a high-pressure mercury lamp to give the aziridine **124**. Reduction of **124** with sodium borohydride in methanol yielded the alcohol **125** stereoselectively, which was further converted to the *cis*-benzindenoazepine **126** by treatment with *p*-toluenesulfonic acid in methanol, followed by methylation with methyl iodide. Successive mesylation of **126** and reduction of the mesylate afforded (\pm)-fumaritrine (**127**) in 71% yield. Thus the conversion of berberines to benzindenoazepines was successfully accomplished by the formation of aziridine derivatives as key intermediates by photochemical valence tautomerization.



SCHEME 25

3. Lahorine and Lahoramine

The indenobenzazepine alkaloids lahorine (**131b**) and lahoramine (**131a**) found in *Fumaria parviflora* Lam. are probably derived from spirobenzylisoquinolines biogenetically.⁴⁷ The conversion of dihydrofumariline (**128b**) and dihydroparfumidine (**128a**) to **131b** and **131a** by treatment with methanesulfonyl chloride and triethylamine in dry tetrahydrofuran, followed by iodine oxidation, involves the aziridinium salts **129a** and **129b** and the quinone methide cations **130a** and **130b** as intermediates (Scheme 26).



SCHEME 26

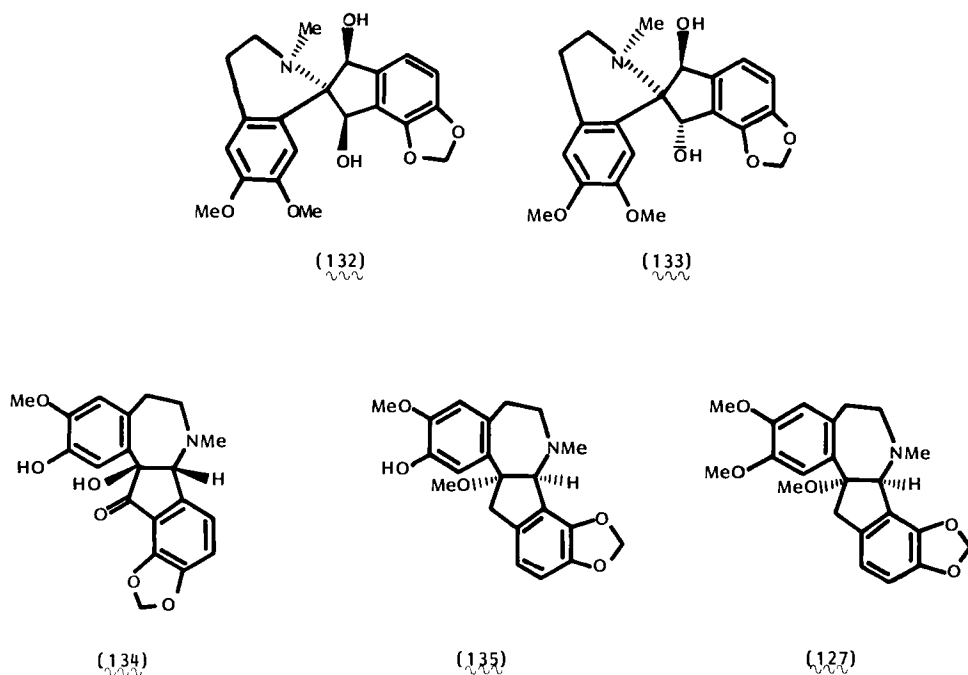
The similar conversion of the spirobenzylisoquinoline alkaloids to indenobenzazepine-type alkaloids led to the stereocontrolled syntheses of (±)-rad-deanine (**132**) and (±)-yenusomine (**133**)⁴⁸ and the structure revision of

⁴⁶ M. Hanaoka, M. Iwasaki, S. Sakurai, and C. Mukai, *Tetrahedron Lett.* **24**, 3845 (1983).

⁴⁷ G. Blaskó, S. F. Hussain, A. J. Freyer, and M. Shamma, *Tetrahedron Lett.* **22**, 3127 (1981).

⁴⁸ G. Blaskó, N. Murugesan, A. J. Freyer, D. J. Gula, B. Şener, and M. Shamma, *Tetrahedron Lett.* **22**, 3139 (1981).

fumarofine (134),⁴⁹ fumaritridine (135),⁵⁰ and fumaritrine (127) (Scheme 27).⁵⁰



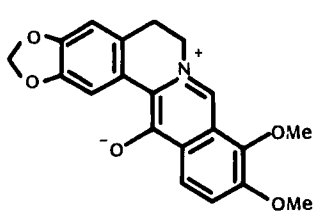
SCHEME 27

An efficient conversion of berberine to a rheadine via an aziridine was also reported independently by Shamma (Scheme 28).⁵¹ Irradiation of berberinephenolbetaine (136), containing aqueous formaldehyde and a little rose bengal, afforded the indenobenzazepine derivative (138) (60%) via the ketoaziridine 137. Reduction of 138 with sodium cyanoborohydride in the presence of dry methanolic hydrogen chloride afforded the keto alcohol 139, periodate oxidation of which furnished the γ -lactone 140. Sodium borohydride reduction of 140, followed by acid treatment, gave the δ -lactone 141, which was further converted to the *cis*-rheadine derivative 142 by reduction and O-methylation.

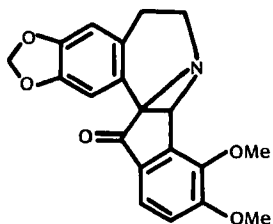
⁴⁹ G. Blaskó, N. Murugesan, S. F. Hussaine, R. D. Minard, M. Shamma, B. Şener, and M. Tanker, *Tetrahedron Lett.* **22**, 3135 (1981).

⁵⁰ G. Blaskó, N. Murugesan, A. J. Freyer, R. D. Minard, and M. Shamma, *Tetrahedron Lett.* **22**, 3143 (1981).

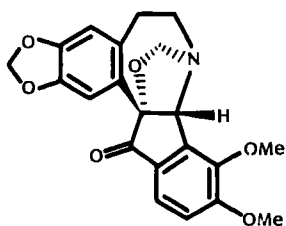
⁵¹ N. Murugesan, G. Blaskó, R. D. Minard, and M. Shamma, *Tetrahedron Lett.* **22**, 3131 (1981).



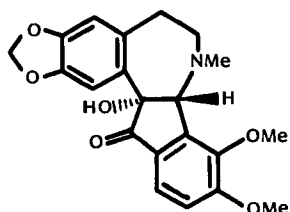
(136)



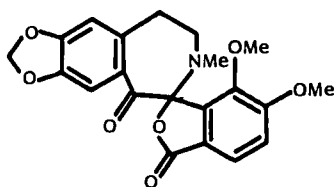
(137)



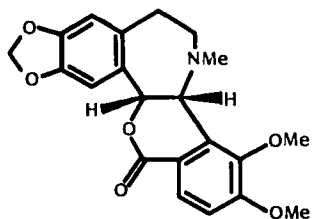
(138)



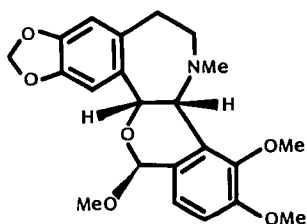
(139)



(140)



(141)



(142)

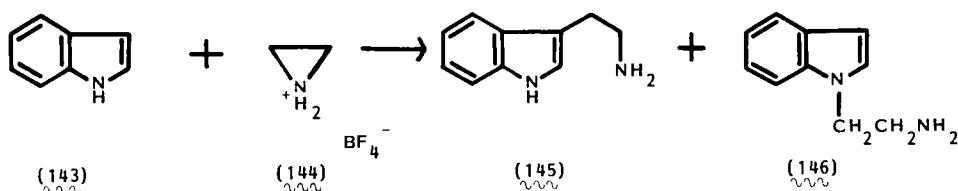
SCHEME 28

The ketoaziridine **137** was also transformed into the indenobenzazepines by the ring opening of the aziridine with acid,⁵² and this conversion provided the general transformation of berberines into rheadan and indenobenzazepine alkaloids.

III. Syntheses of Indole Alkaloids

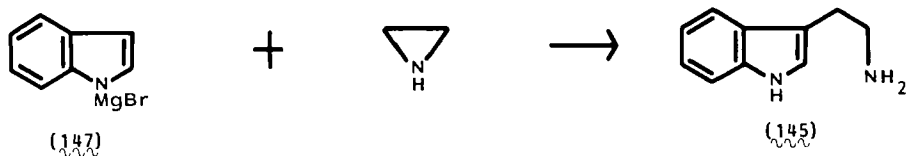
A. TRYPTAMINE AND ITS DERIVATIVES

The most convenient syntheses of tryptamines involve treatment of indole with aziridines. The reaction of indole (**143**) with aziridinium tetrafluoroborate (**144**) afforded tryptamine (**145**) in 40% yield (Scheme 29). However, lack of regioselectivity in this reaction⁵³ gives 1-(2-aminoethyl)indole (**146**) as a by-product.



SCHEME 29

The treatment of the magnesium derivative of indole (**147**) with aziridine in refluxing xylene led to tryptamine (**145**) (46%) (Scheme 30).⁵⁴



SCHEME 30

The synthesis of tryptamines by Mannich reactions involves the aziridinium salt as an intermediate.⁵⁵ For instance, the reaction of indole (**143**) with chloroacetaldehyde (**148**) in the presence of a secondary amine afforded

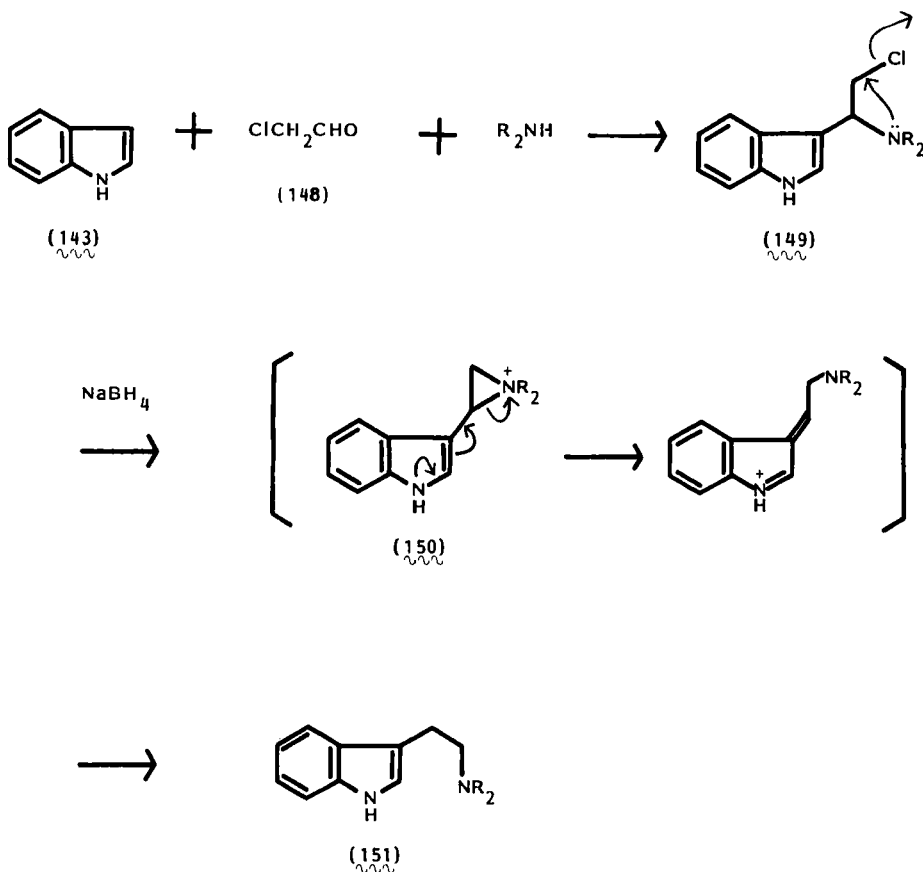
⁵² G. Blaskó, V. Elango, N. Murugesan, and M. Shamma, *Chem. Commun.*, 1246 (1981).

⁵³ E. Pfeil and U. Harder, *Angew. Chem., Int. Ed. Engl.* **6**, 178 (1967); cf. E. P. Styngach, F. S. Rivilis, N. M. Frolova, K. S. Khariton, and A. A. Semenov, *Khim. Geterotsikl. Soedin.*, 1066 (1974).

⁵⁴ R. Bucourt and M. Vignan, *Bull. Soc. Chim. Fr.*, 1190 (1961); R. Bucourt, J. Valls, and R. Joly, U.S. Patent 2,920,080 (1960) [*CA* **54**, 13018 (1960)].

⁵⁵ M. Julia, J. Bagot, and O. Siffert, *Bull. Soc. Chim. Fr., Part II*, 1424 (1973).

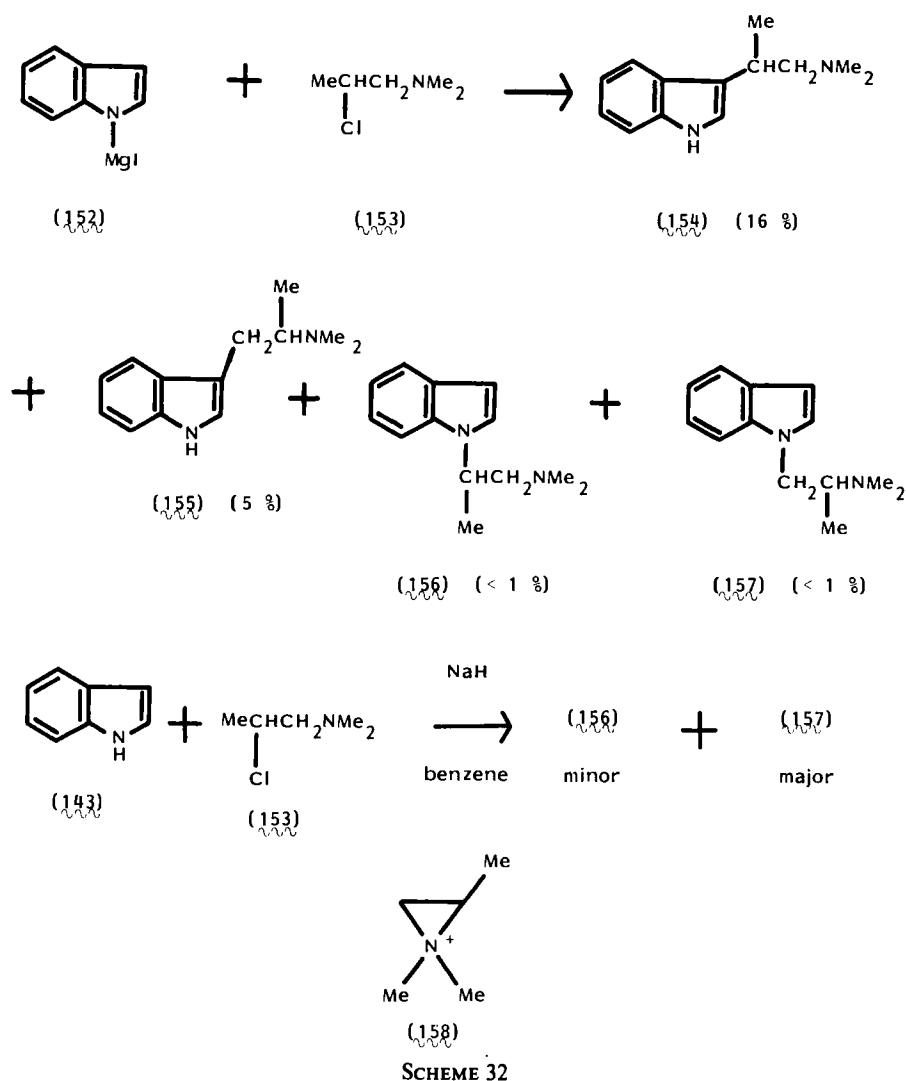
the gramine derivative **149**, whose reduction with sodium borohydride afforded the tryptamine derivative **151**, probably via the aziridinium salt **150** (Scheme 31).



SCHEME 31

Similar results have been obtained from the reaction of β -dialkylaminopropyl halides with indole derivatives (Scheme 32).⁵⁶ Alkylation of indolylmagnesium iodide (**152**) with 2-chloro-1-dimethylaminopropane (**153**) furnished the four products **154**–**157**, whereas the reaction of the sodium salt of indole with **153** yielded the rearranged compound **157** as a major product, accompanied by **156**. These results suggested that the aziridinium salt **158** is involved in this alkylation reaction as an intermediate.

⁵⁶ C. R. Ganellin, D. R. Hollyman, and H. F. Ridley, *J. Chem. Soc. C*, 2220 (1967).

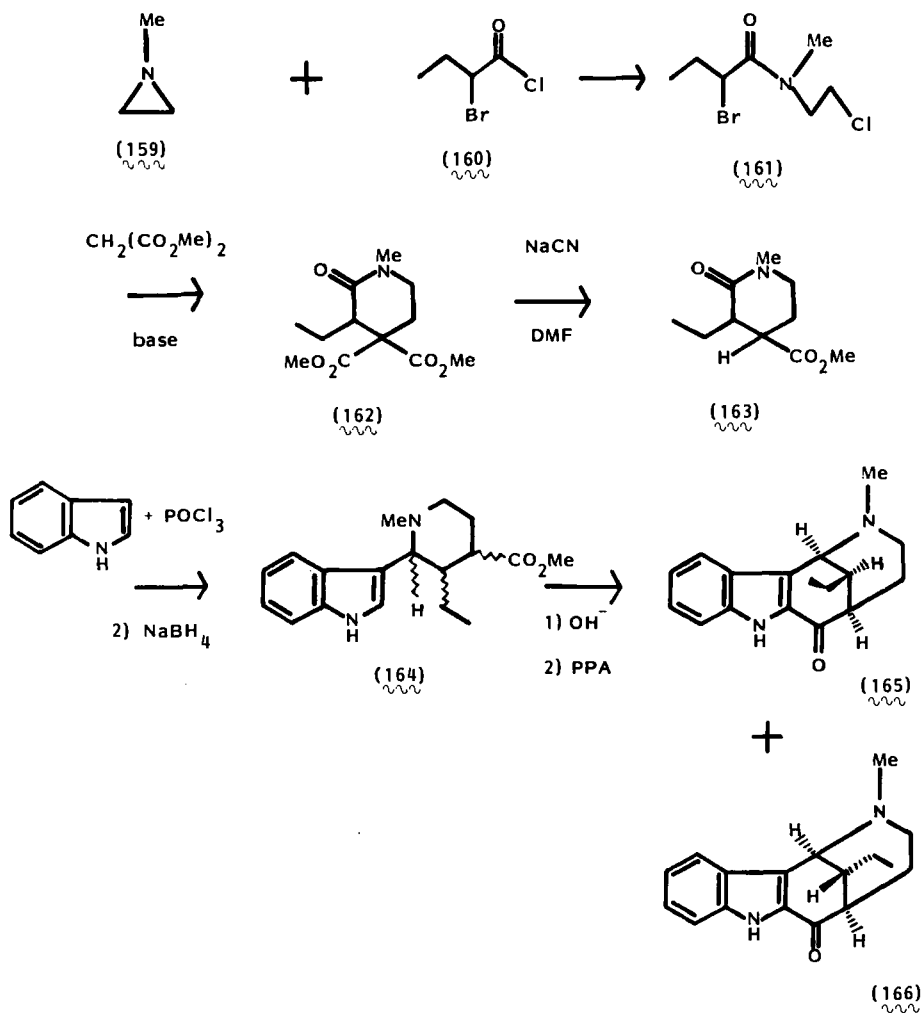


B. DASYCARPIDONE AND EPIDASYCARPIDONE

Acylating ring opening of *N*-methylaziridine is a key feature of the synthesis of dasycarpidone⁵⁷ (165) and epidasycarpidone (166) (Scheme 33). The reaction of *N*-methylaziridine (159) with α -bromobutyryl chloride (160)

⁵⁷ L. J. Dolby and H. Biere, *J. Am. Chem. Soc.* **90**, 2699 (1968).

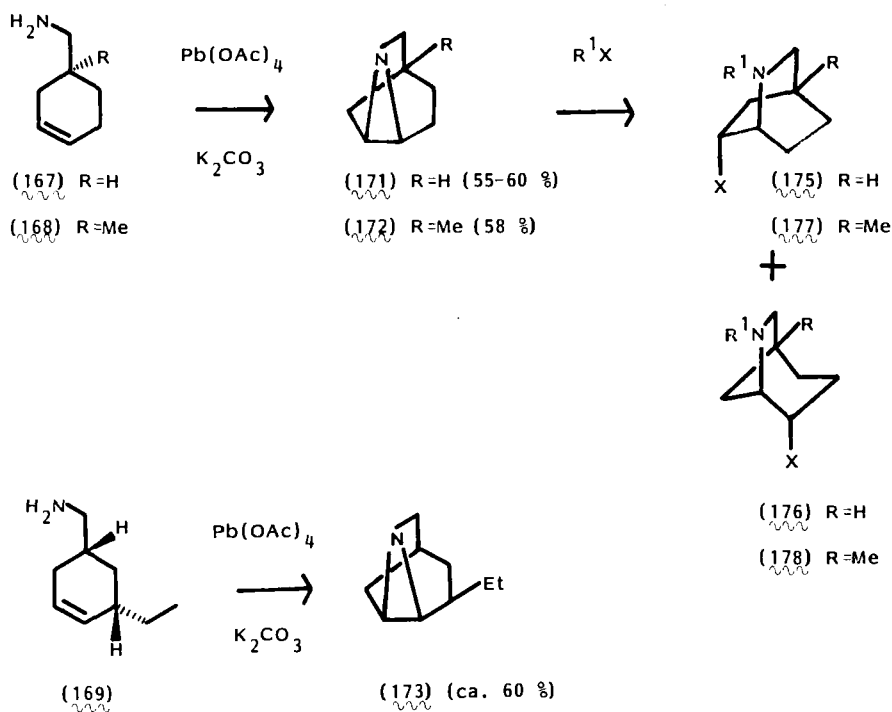
provided the ring-opened amide **161**, whose treatment with malonate in the presence of base produced 2-piperidone derivative **162**. After decarbomethoxylation of **162** with sodium cyanide in *N,N*-dimethylformamide, piperidone **163** was attached to indole by a Vilsmeier condensation, followed by reduction with sodium borohydride to provide the 3-substituted indole **164**. Hydrolysis of the ester group of **164** and subsequent ring closure of the resulting acid to the α -indole position with polyphosphoric acid yielded a mixture of dasycarpidone (**165**) and epidasycarpidone (**166**). Unfortunately, the major product in this synthesis was epidasycarpidone (**166**).



SCHEME 33

C. IBOGAMINE AND CORONARIDINE

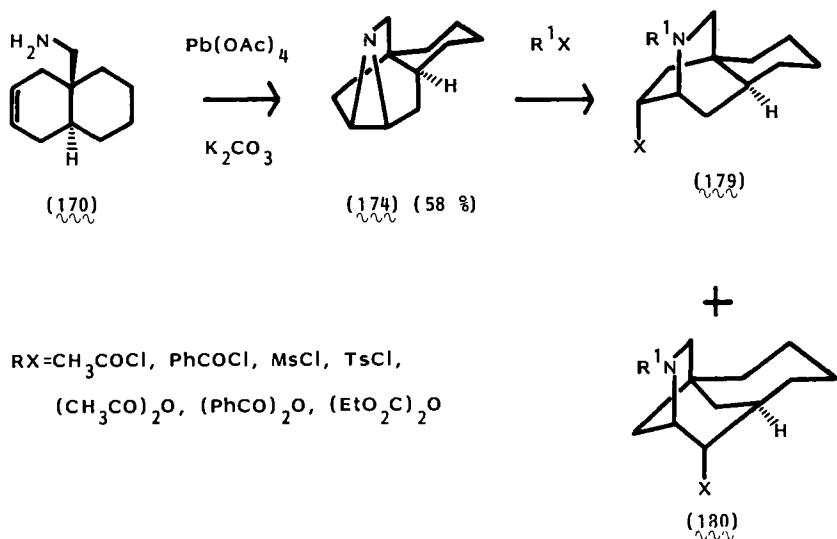
Construction of an isoquinuclidine ring system employing intramolecular aziridine formation of olefinic amines and subsequent ring opening has been reported by Nagata and co-workers⁵⁸ (Scheme 34). Thus, the oxidative cyclization of the olefinic primary amines **167**–**170** with lead tetraacetate in benzene afforded the aziridines **171**–**174** (55–60%). The ring-opening reaction of **171** with an acylating agent brought about the formation of an isoquinuclidine derivative (**175**) along with **176** in the ratio of ~4:1. Similarly, conversion of **172** and **174** with various acylating reagents provided the expected isoquinuclidine derivatives **177** and **179** predominantly, accompanied by the isomers **178** and **180**.



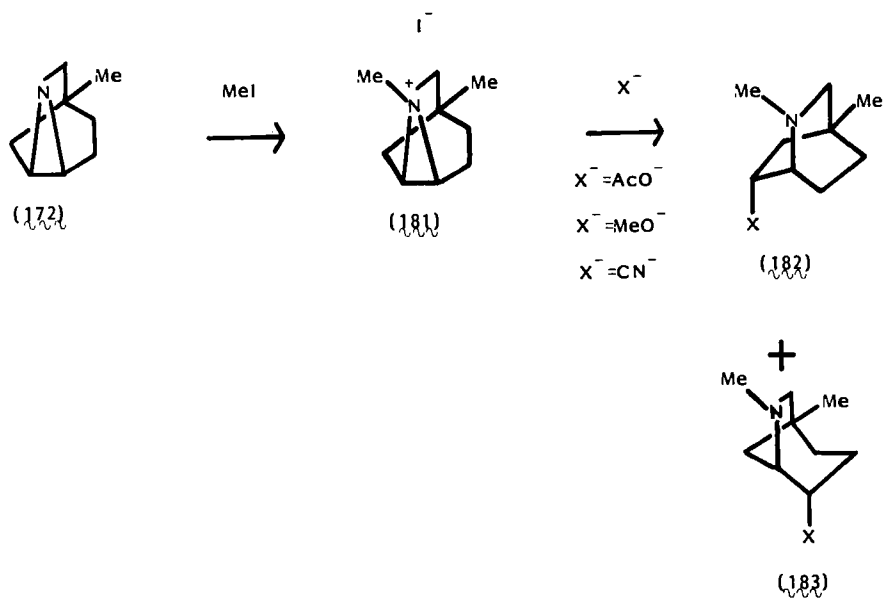
SCHEME 34

Furthermore, the ring opening of the aziridinium salt **181**, prepared from the aziridine **172** with methyl iodide at low temperature, by reaction with a number of nucleophiles also yielded the isoquinuclidine derivatives **182** predominantly, together with the isomer **183** (Scheme 35).

⁵⁸ W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.* **89**, 5046 (1967); cf. P. S. Portoghesi and D. T. Sepp, *Tetrahedron* **29**, 2253 (1973).



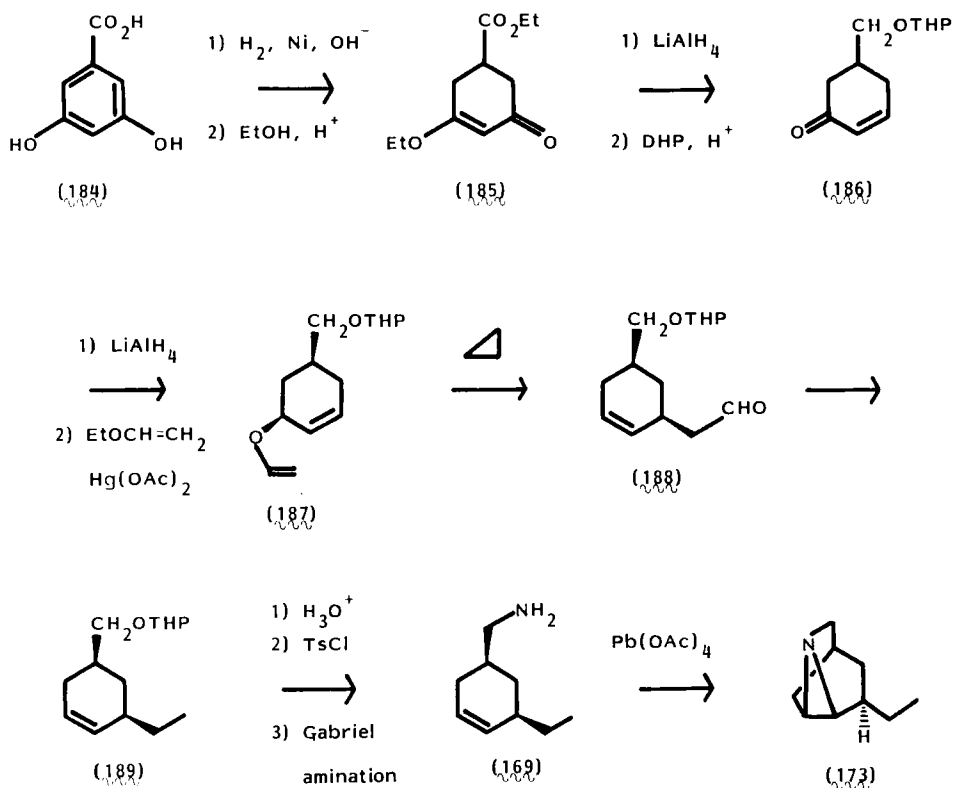
SCHEME 34 (continued)



182:183 = 2-3:1

SCHEME 35

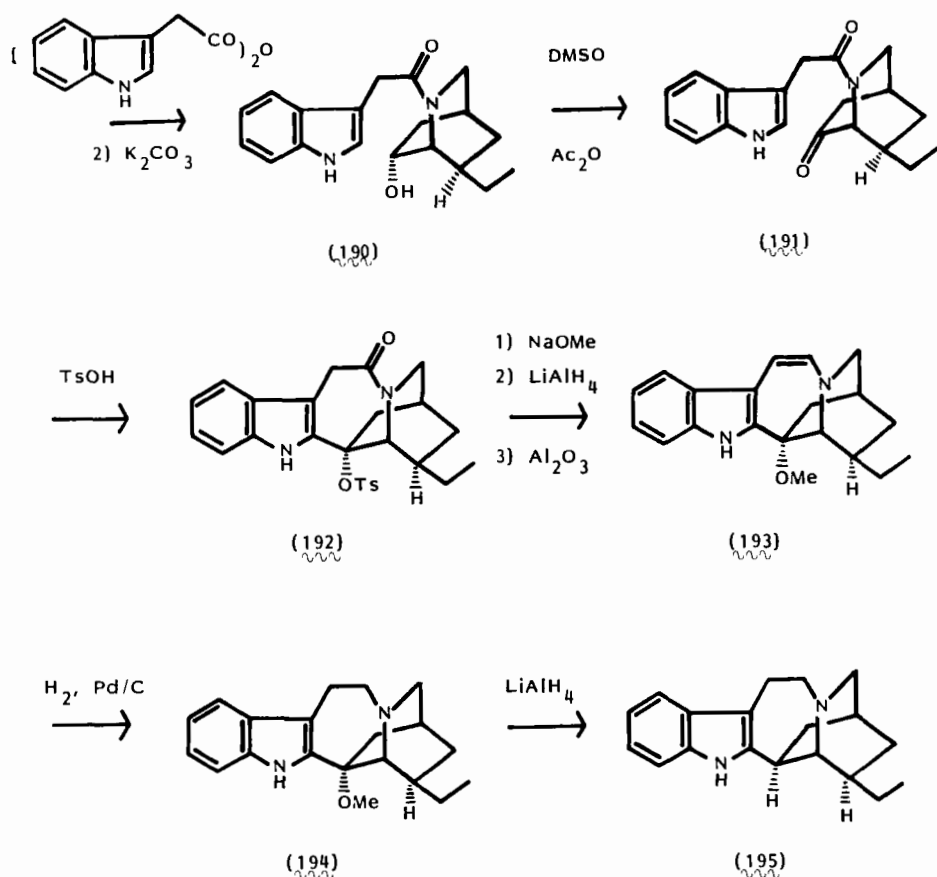
These reactions were successfully applied to the synthesis of the indole alkaloids (\pm)-ibogamine (**195**)⁵⁹ and (\pm)-coronaridine (**201**).⁶⁰ The aziridine **173**, a key intermediate in this synthesis, was prepared as follows. Reduction of 3,5-dihydroxybenzoic acid (**184**), followed by esterification gave the ester **185**, which was converted to the enone **186** by lithium aluminum hydride and subsequent protection of the primary alcohol with dihydropyran. The enone **186** was again reduced with lithium aluminum hydride to afford the enol, stereoselectively, whose Claisen rearrangement via the ether **187** furnished the aldehyde **188** with the desired stereochemistry. Huang–Minlon reduction of **188** gave **189**, whose successive deprotection with acid, tosylation, and Gabriel amination afforded the primary amine **169**. Oxidative aziridine formation of the amine **169** with lead tetraacetate led to the synthesis of the desired aziridine **173** in about 60% yield. With the key compound in hand, the ring-opening reaction was then studied. Treatment of the aziridine



SCHEME 36

⁵⁹ W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *J. Am. Chem. Soc.* **90**, 1650 (1968).

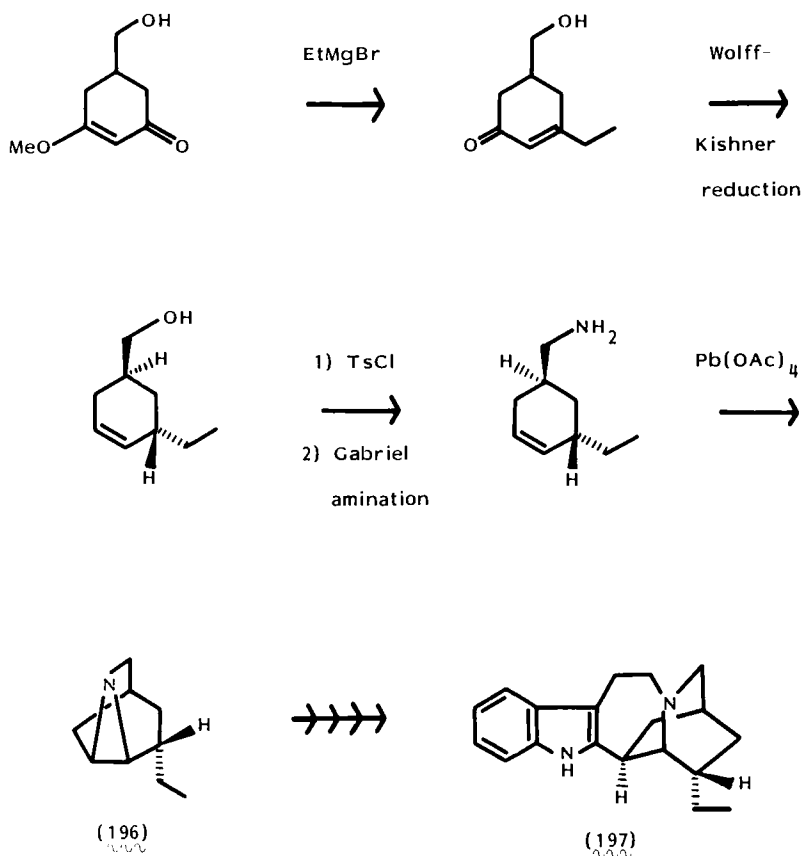
⁶⁰ S. Hirai, K. Kawata, and W. Nagata, *Chem. Commun.*, 1016 (1968).



SCHEME 36 (continued)

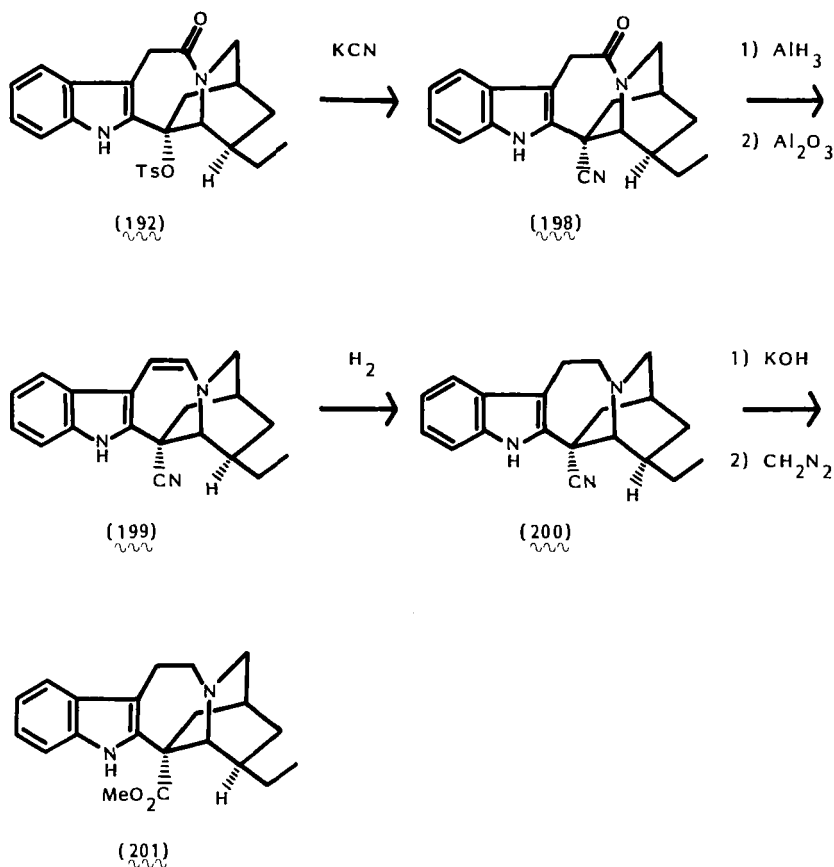
173 with indolylacetic anhydride, followed by hydrolysis with potassium carbonate in methanol, gave rise to the isoquinuclidine derivative **190**; no isomer was isolated. Oxidation of **190** with dimethyl sulfoxide and acetic anhydride gave the ketone **191**, whose treatment with p -toluenesulfonic acid furnished the tosylate **192**. The conversion of the iboga derivative **192** to (±)-ibogamine (**195**) was accomplished by five steps as follows. A substitution reaction of the tosylate group of **192** with methoxide anion, followed by reduction and dehydration, furnished the olefin **193**, whose catalytic reduction over palladium on carbon gave the amine **194**. Finally, (±)-ibogamine (**195**) was obtained from **194** by lithium aluminum hydride reduction. Thus the efficient synthesis of (±)-ibogamine (**195**) was achieved, involving an ingenious preparation of the isoquinuclidine nucleus by acylation of a bridged aziridine (see Scheme 36).

Epiibogamine (**197**) was also synthesized from the aziridine **196** by adopting the above synthetic strategy as outlined in Scheme 37.



SCHEME 37

As an extension of the above work, 7-oxo-18-tosyloxyibogamine (**192**) was further transformed into (\pm)-coronaridine (**201**) (Scheme 38). Treatment of **192** with potassium cyanide in boiling acetonitrile for 15 h afforded the cyanide **198**, whose reduction with an excess of AlH_3 at -70°C , followed by dehydration of the resulting carbinolamine using alumina, provided the enamine **199** in 87% yield. Catalytic hydrogenation of **199** gave the amine **200**, which was then hydrolyzed with potassium hydroxide in diethylene glycol at 160°C , followed by acidification and esterification with diazo-methane, to produce (\pm)-coronaridine (**201**) in 46% yield. An improved synthesis of (\pm)-ibogamine (**195**) from the key intermediate **192** by AlH_3 reduction was also achieved in 37–46% yield.



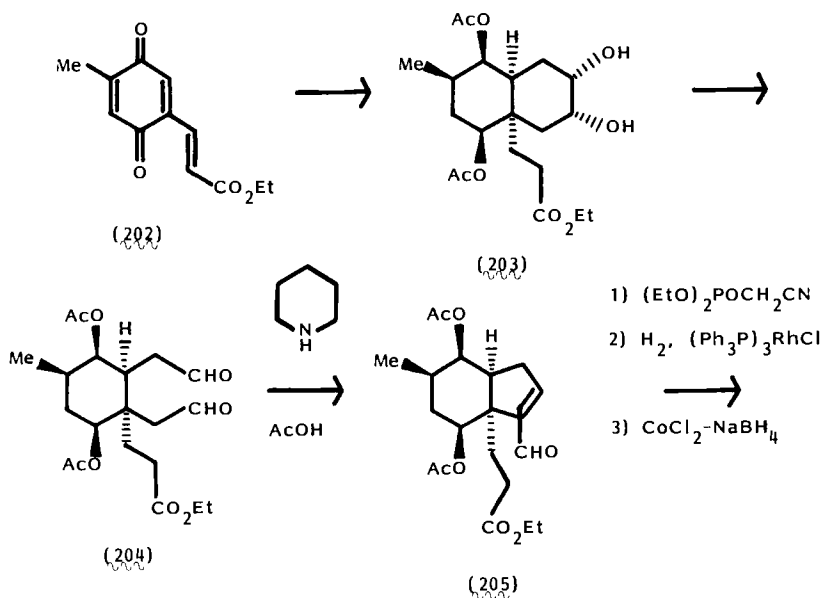
SCHEME 38

IV. Miscellaneous

A. SERRATININE

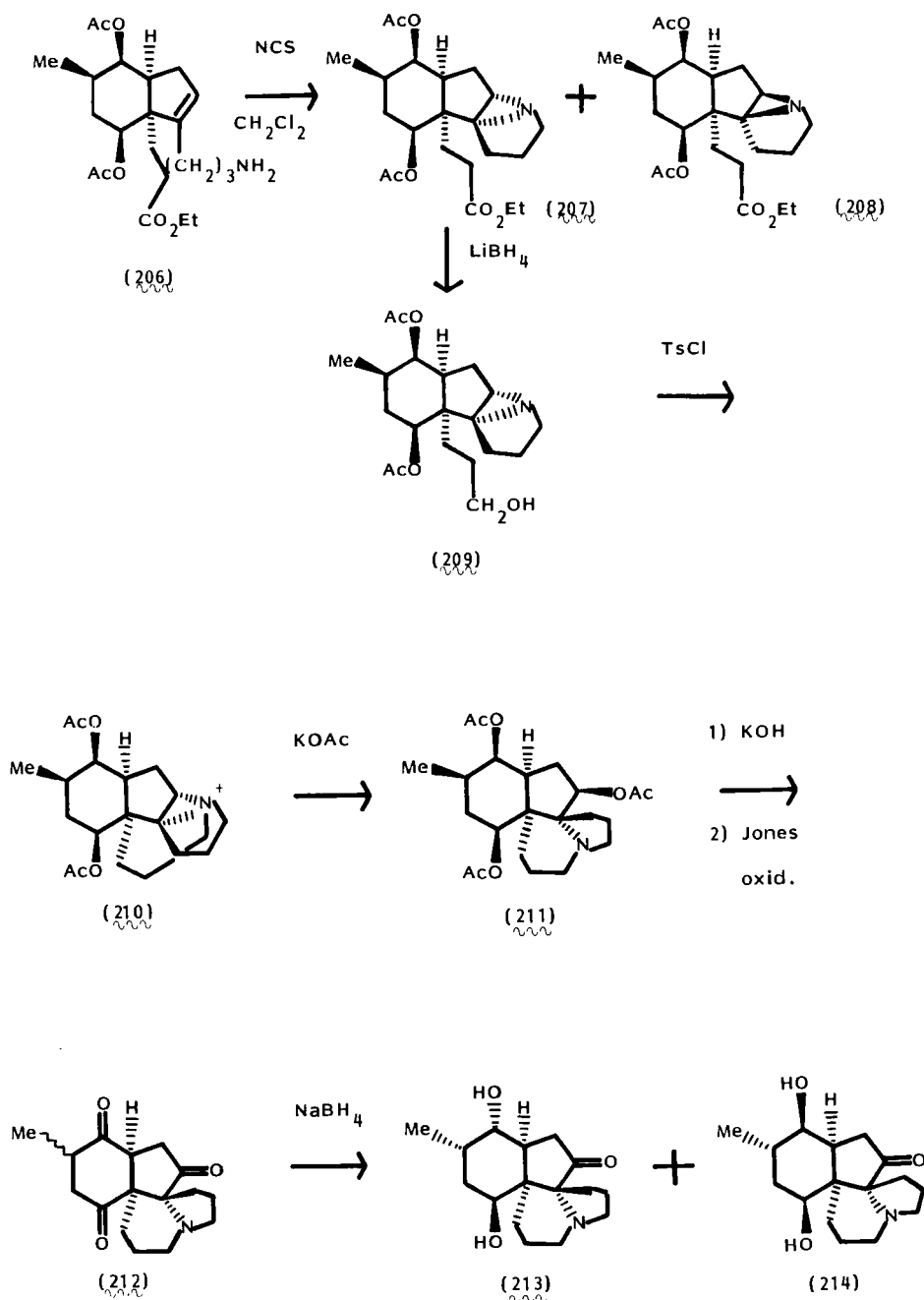
Serratinine has a unique skeleton bearing two adjacent quaternary carbon atoms and has complicated stereochemistry. An intramolecular oxidative aziridine formation and its subsequent ring-opening reaction has been utilized to construct an indolizidine ring system, present in the lycopodium alkaloid serratinine. Diels-Alder reaction of the ester **202** with butadiene, followed by Zn-AcOH reduction, NaBH₄ reduction, acetylation, OsO₄-NaClO₃ oxidation, and catalytic hydrogenation afforded the diol **203**, whose glycol cleavage with periodic acid furnished the dialdehyde **204**. Selective aldol cyclization of **204** by treatment with an excess of pyrrolidine and acetic

acid in methanol provided the aldehyde **205**, Wittig reaction of which with diethyl cyanomethylphosphate and sodium hydride gave the conjugated nitrile. Catalytic hydrogenation of the nitrile over $(\text{Ph}_3\text{P})_3\text{RhCl}$ in benzene, followed by selective reduction of a cyano group with $\text{NaBH}_4 - \text{CoCl}_2$ afforded the primary amine **206**. An oxidative cyclization of the amine **206** with *N*-chlorosuccinimide and Cu_2Cl_2 brought about the formation of the aziridine ring to provide **207** and **208** in 20 and 3% yields, respectively. Since the aziridine formation was assumed to occur from the convex face, preferentially, the stereochemistry of the major product was assigned to be **207**. The primary alcohol **209** was obtained from the ester **207** by selective reduction with LiBH_4 in 74% yield. Treatment of **209** with tosyl chloride in pyridine gave the aziridinium salt **210**, which was then subjected to the ring-opening reaction of aziridine with potassium acetate in ethanol to provide the expected triacetate **211**, bearing all the carbon framework for serratinine and an oxygen function on the B ring, in 33% yield from **209**. Hydrolysis of **211** with methanolic potassium hydroxide and subsequent Jones oxidation yielded the triketone **212**. Finally, reduction of **212** with sodium borohydride afforded (\pm)-serratinine (**213**) and (\pm)-8-episerratinine (**214**) in 18% and 25% yields, respectively.⁶¹ Thus the stereocontrolled synthesis of the lycopodium alkaloid (\pm)-serratinine was accomplished by employing an intramolecular oxidative aziridine formation as a key step (Scheme 39).



SCHEME 39

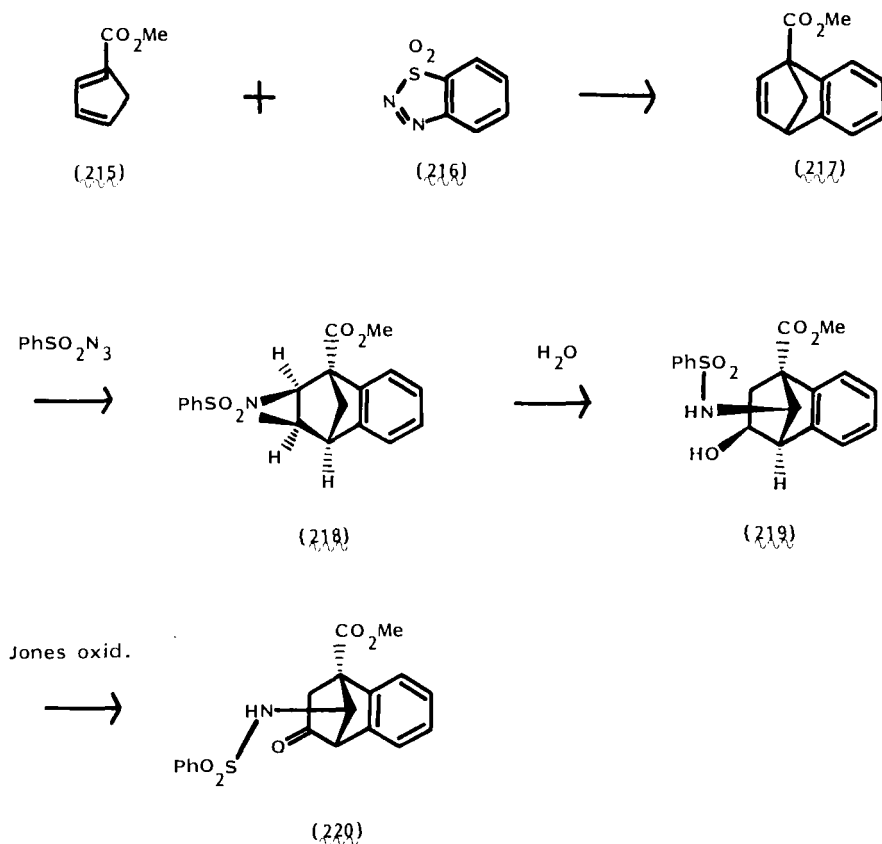
⁶¹ T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Commun.*, 827 (1974); *Chem. Pharm. Bull.* **23**, 1511 (1975).



SCHEME 39 (continued)

B. DITERPENE ALKALOIDS

Fascinating rearrangements of aziridines have been applied to the synthesis of diterpene alkaloids by Wiesner and co-workers⁶² (Scheme 40). For example, the ester **217**, prepared from cyclopentadiene carboxylate (**215**) and the benzyne precursor **216** by a Diels–Alder reaction, was converted to the aziridine **218** by treatment with benzenesulfonyl azide in 83% yield. When the aziridine **218** was heated with water for 24 h, the hydroxy ester **219** was obtained in 97% yield; subsequent oxidation with the Jones reagent afforded the ketone **220**. This rearrangement is analogous to that of the benzenesulfonylaziridine of norbornene.⁶³

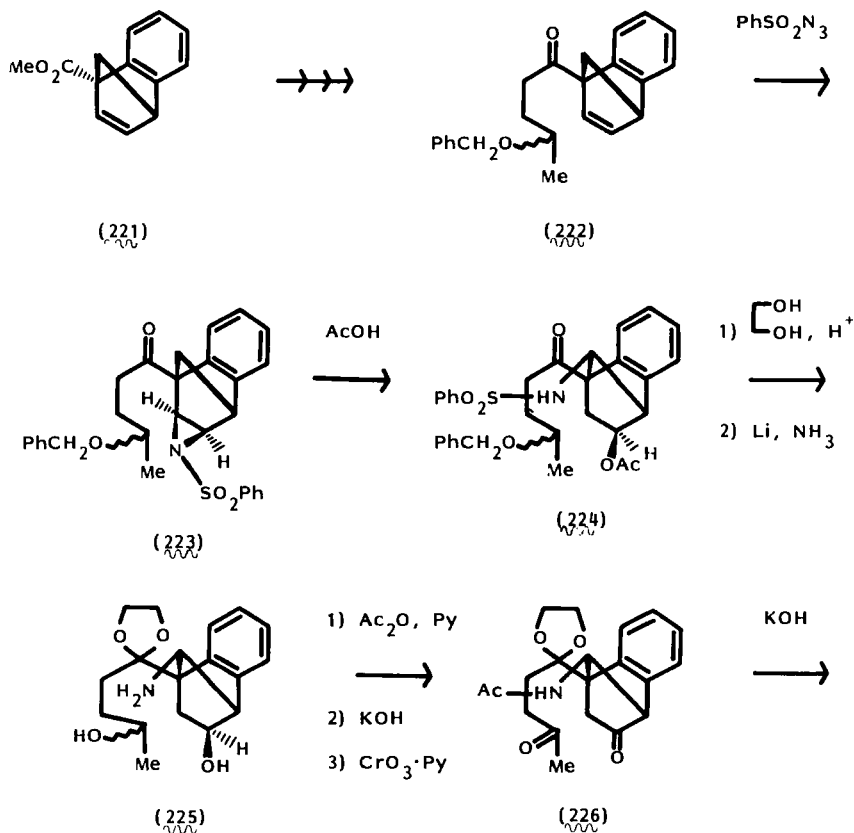


SCHEME 40

⁶² K. Wiesner and A. Philipp, *Tetrahedron Lett.*, 1467 (1966); K. Wiesner, P. Ho, R. C. Jain, S. F. Lee, S. Oida, and A. Philipp, *Can. J. Chem.* **51**, 1448 (1973).

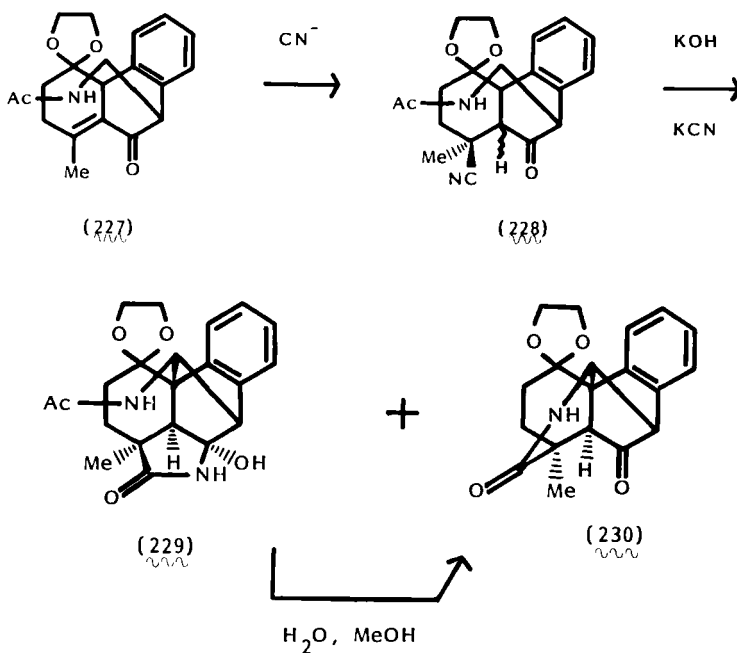
⁶³ J. E. Franz, C. Osuch, and M. W. Dietrich, *J. Org. Chem.* **29**, 2922 (1964).

The ketone **220** obtained above is important for the synthesis of the diterpene alkaloid songorine. Studies on the above reaction led to the stereospecific synthesis of pentacyclic intermediates⁶⁴ with a bridge in ring B of the delphinine-type diterpene alkaloids (Scheme 41). The ketone **222**, derived from the ester **221** by several steps, was converted to the aziridine **223** (64%) by treatment with an excess of benzenesulfonyl azide as described above. The rearrangement of the aziridine **223** to the amine **224** was achieved by heating with an excess of glacial acetic acid at 100°C for 45 min, in 49% yield. After protection of the carbonyl function with ethylene glycol, the sulfonyl group of the product was cleaved by treatment with lithium metal in liquid ammonia to give the diol **225**, whose successive acetylation, hydrolysis, and oxidation with the Jones reagent afforded the amide **226**. The intramolecular aldol condensation of **226** gave the enone **227**, which was further con-



SCHEME 41

⁶⁴ K. Wiesner, A. Philipp, and P. Ho, *Tetrahedron Lett.*, 1209 (1968).



SCHEME 41 (continued)

verted to a mixture of the stereoisomeric cyanides **228** by a hydrocyanation reaction. The hydrolysis of **228** with potassium hydroxide and potassium cyanide in refluxing 10% water–methanol furnished the lactamol **229** and the lactam **230** in the ratio of 5 : 3. The former compound (**229**) was easily converted to the latter by treatment with potassium hydroxide in 60% yield.

The preparation of the key intermediate **231** for the synthesis of songorine (**232**) was also reported by the same author based on the same synthetic strategy as described above (Scheme 42).^{65–67}

Further synthetic studies of diterpene alkaloids with the aziridine rearrangement as a key reaction have been reported^{68–70} and led to the synthesis of diterpene alkaloids chasmanine (**234**) and 13-deoxydelphonine (**235**).

⁶⁵ P. Ho, S. Oida, and K. Wiesner, *Chem. Commun.*, 883 (1972).

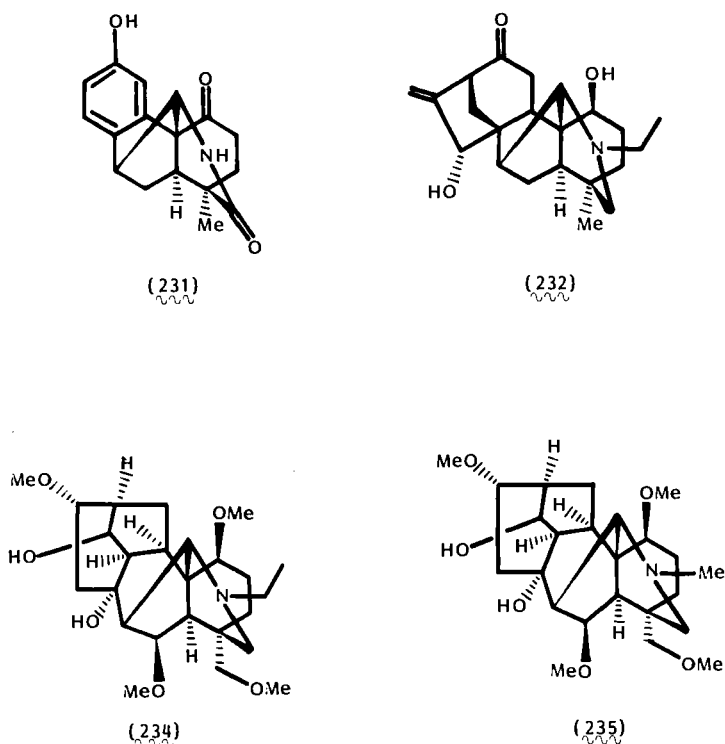
⁶⁶ K. Wiesner, P. Ho, D. Chang, and J. F. Blount, *Experientia* **28**, 766 (1972).

⁶⁷ K. Wiesner, P. Ho, D. Chang, Y. K. Lam, C. S. J. Pan, and W. Y. Ren, *Can. J. Chem.* **51**, 3978 (1973).

⁶⁸ K. Wiesner, P. Ho, and S. Oida, *Can. J. Chem.* **52**, 1042 (1974).

⁶⁹ S.-F. Lee, G. M. Sathe, W. W. Sy, P. Ho, and K. Wiesner, *Can. J. Chem.* **54**, 1039 (1976).

⁷⁰ T. Y. R. Tsai, K. P. Nambiar, D. Krikorian, M. Botta, R. Marini-Bettolo, and K. Wiesner, *Can. J. Chem.* **57**, 2124 (1979).



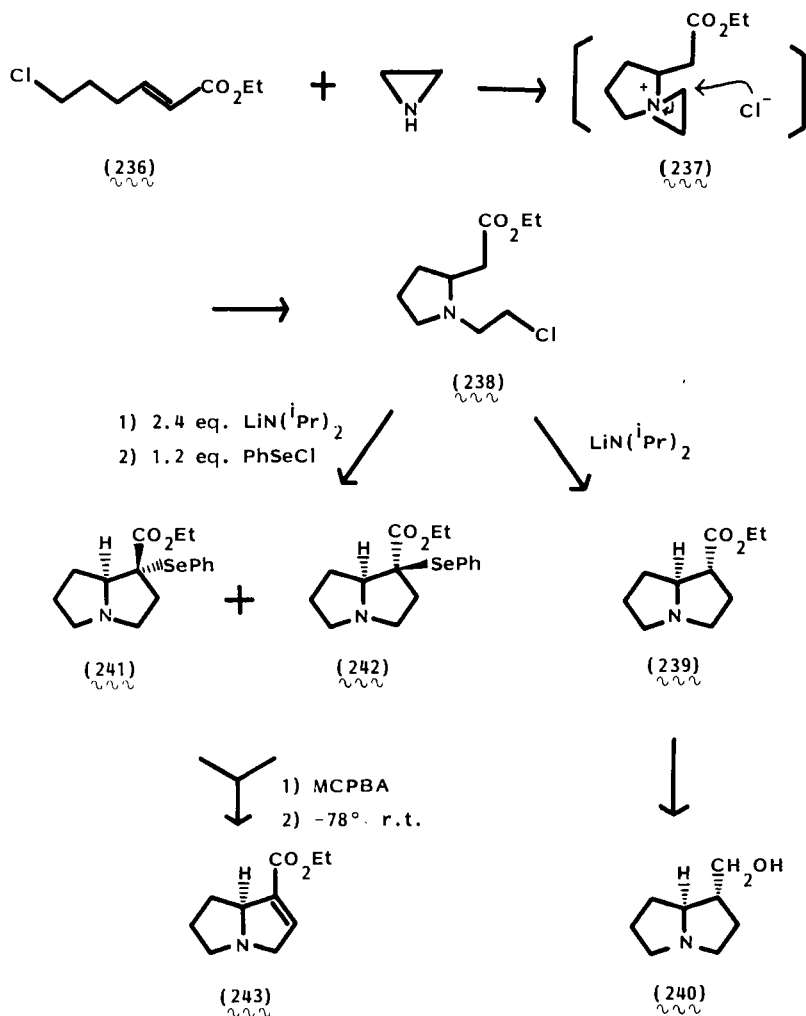
SCHEME 42

C. PYRROLIZIDINE ALKALOIDS

Pyrrolizidine alkaloids (\pm)-trachelanthamidine (**240**) and (\pm)-supinidine (**244**) were synthesized,⁷¹ based on the Michael addition of an aziridine to an α,β -unsaturated ester and subsequent ring opening of an aziridinium intermediate. Interest in these alkaloids stems from their biological activities. Treatment of ethyl 6-chloro-2-hexenoate (**236**) with excess aziridine at 0°C gave the pyrrolidine derivative **238** in one step, probably via the aziridinium salt **237** in 73% yield. The intramolecular cyclization of **238** with lithium diisopropylamide in tetrahydrofuran provided the thermodynamically more stable ester **239** as the sole product, (86%), which was then converted to (\pm)-trachelanthamidine (**240**) by reduction with lithium aluminum hydride. Since necine bases must contain a 1,2-didehydro system in their molecule to exhibit physiological activity, the following reactions were carried out to introduce a 1,2-didehydro system. Treatment of **238** with 2.4 equiv of lith-

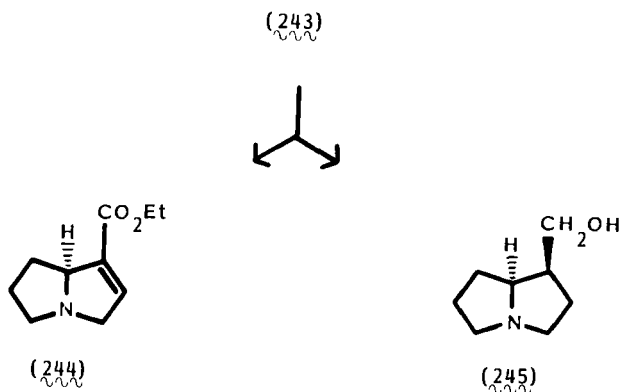
⁷¹ T. Kametani, K. Higashiyama, H. Otomasu, and T. Honda, *Heterocycles* **22**, 729 (1984).

ium diisopropylamide, followed by the addition of 1.2 equiv of phenylselenenyl chloride gave the two selenides **241** and **242**; both were converted to the same α,β -unsaturated ester (**243**) as expected. Therefore, the selenides **241** and **242** were unambiguously assigned to be diastereoisomers at the C-1 position. Since lithium aluminum hydride reduction of **243** has already been carried out by Robins⁷² to produce (\pm)-supinidine (**244**) and (\pm)-isoretronecanol (**245**), this synthesis constitutes a formal synthesis of these alkaloids (Scheme 43). This short and novel synthesis should provide a general synthetic route for this class of alkaloids.



SCHEME 43

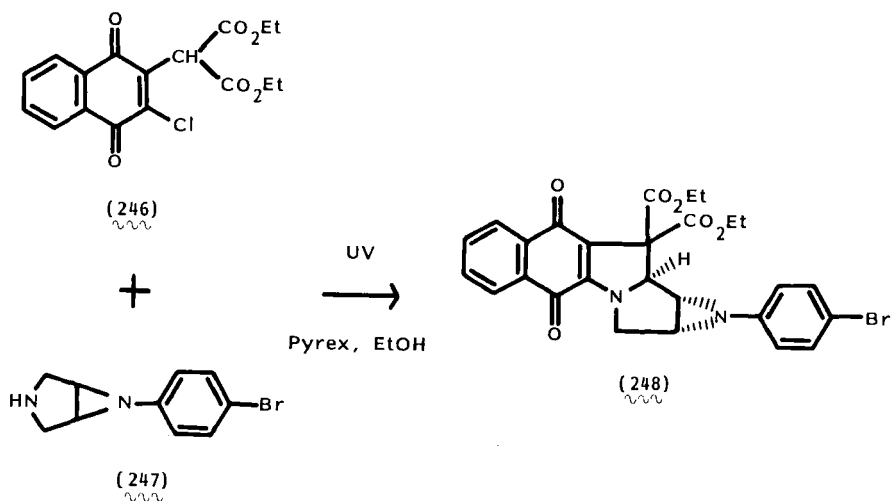
⁷² D. J. Robins and S. Sakdarat, *J. C. S. Perkin I*, 1734 (1979).



SCHEME 43 (continued)

D. MITOMYCIN

The photolysis of quinone derivatives with secondary amines was presumed to involve an aziridine derivative as an intermediate.⁷³ The photochemical reaction of 3-chloro-2-bis(ethoxycarbonyl)methyl-1,4-naphthoquinone (246) with 6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hexane (247) gave aziridinopyrrolo[1,2-*a*]benz[*f*]indoloquinone (248) as a model compound of mitomycin by a one-pot reaction in 63% yield (Scheme 44).⁷⁴

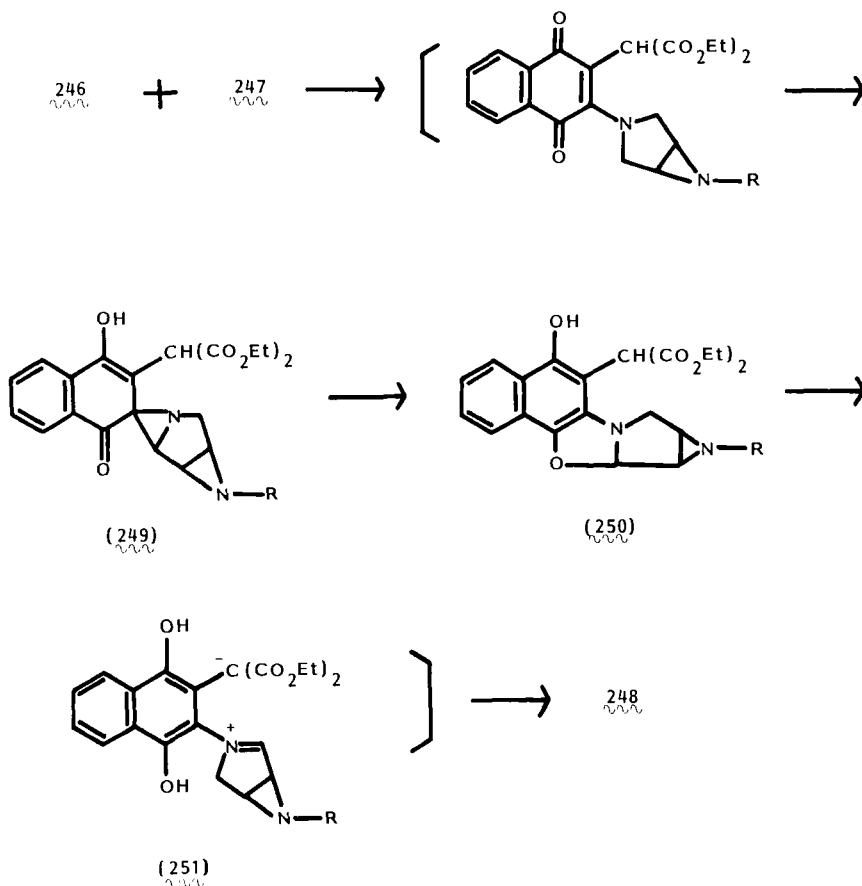


SCHEME 44

⁷³ C. M. Orlando, H. Mark, A. K. Bose, and M. S. Manhas, *J. Org. Chem.* **33**, 2512 (1968).

⁷⁴ M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, *J. Org. Chem.* **43**, 182 (1978); M. Akiba, S. Ikuta, and T. Takada, *Heterocycles* **9**, 813 (1978); M. Akiba, Y. Kosugi, and T. Takada, *ibid.*, 1607.

The reaction was said to proceed through the aziridine **249**, the oxazoline **250**, and the zwitterion intermediate **251**, as shown in Scheme 45.



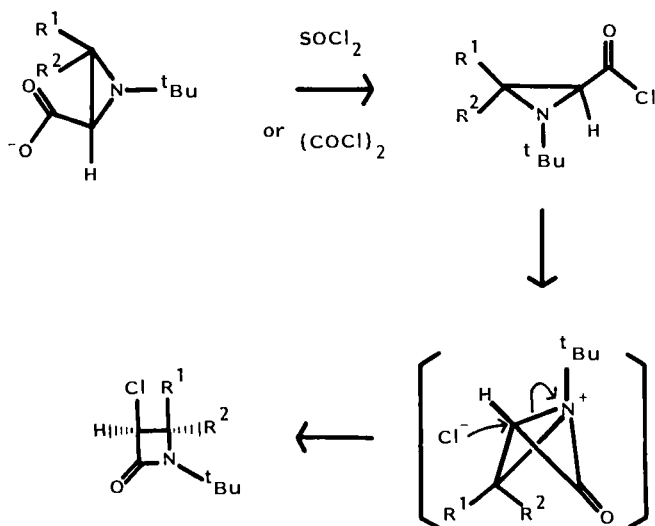
SCHEME 45

E. β -LACTAM

Interconversions of aziridine carboxylates and β -lactams have been achieved.^{75,76} In fact, a variety of carboxylate activating groups convert aziridine carboxylates to 3-halo-2-azetidinones in 20–80% yields (Scheme 46). This reaction is stereospecific and believed to proceed via a 1-azabicyclo[1.1.0]butan-2-one cation.

⁷⁵ J. A. Deyrup and S. C. Clough, *J. Am. Chem. Soc.* **91**, 4590 (1969).

⁷⁶ J. A. Deyrup and S. C. Clough, *J. Org. Chem.* **34**, 902 (1974).



SCHEME 46

Later, β -lactams have been obtained by regiospecific metal-catalyzed ring expansion of aziridines.⁷⁷ Treatment of *N*-*tert*-butyl-2-phenylaziridine (**252**) with carbon monoxide in benzene, employing chlorodicarbonylrhodium(I) dimer as the catalyst at 90°C and 20 atm, produced the azetidinone **253** in quantitative yield. Several other β -lactams were also synthesized from the corresponding aziridine derivatives by the application of this method, and it was noted that this reaction was completely regiospecific. The possible reaction mechanism for the formation of β -lactams is outlined in Scheme 47.

F. MUSCAZONE

The photoinduced transformation of 3-hydroxyisoxazole (**254**) into 2(3*H*)-oxazolone was successfully applied to the synthesis of muscazone (**256**), probably via an intermediate α -lactam (**255**) (Scheme 48).⁷⁸

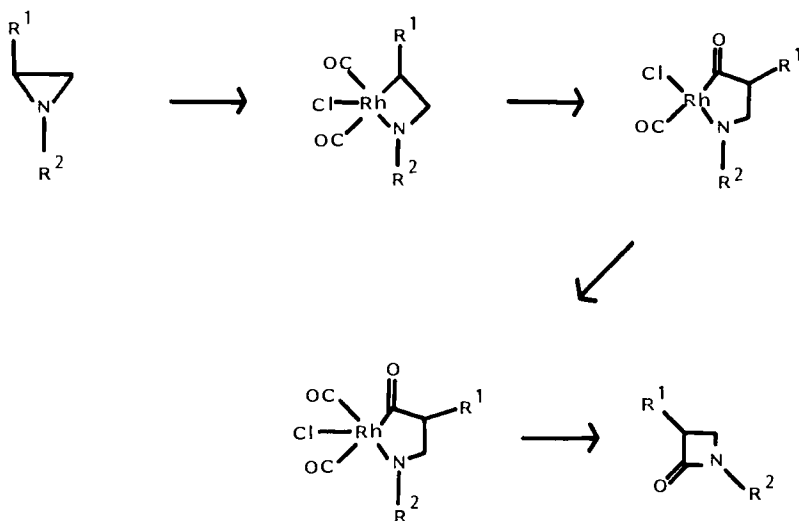
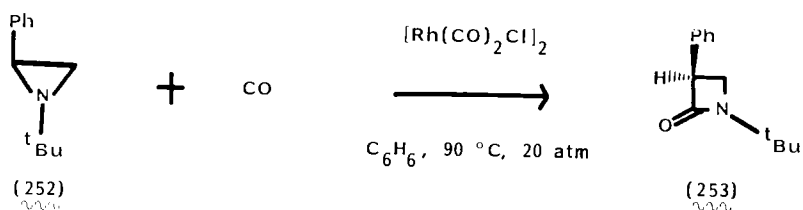
G. (\pm)-PSEUDOCONHYDRINE

One of the hemlock alkaloids, (\pm)-pseudoconhydrine (**261**), was synthesized⁷⁹ from the halomethylpyrrolidine derivative **258**, based on the reported

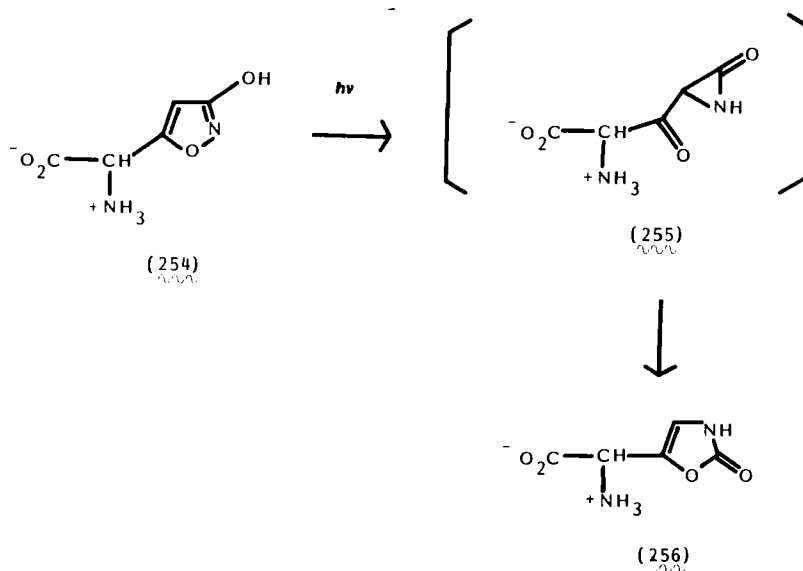
⁷⁷ H. Alper and F. Urso, *J. Am. Chem. Soc.* **105**, 6737 (1983).

⁷⁸ H. Göth, A. R. Gagneux, C. H. Eugster, and H. Schmid, *Helv. Chim. Acta* **50**, 137 (1967).

⁷⁹ K. E. Harding and S. R. Burks, *J. Org. Chem.* **49**, 40 (1984).

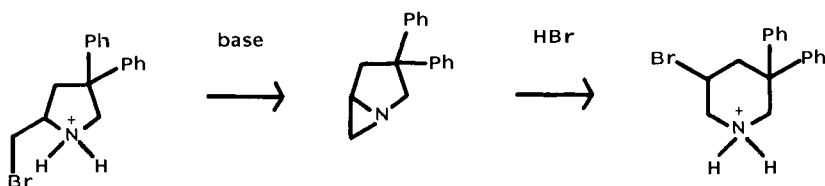


SCHEME 47



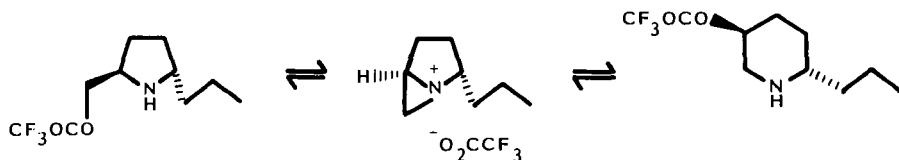
SCHEME 48

conversion⁸⁰ to a 3-substituted piperidine through a bicyclic aziridine intermediate, as illustrated in Scheme 49. The pyrrolidine derivative **258** was



SCHEME 49

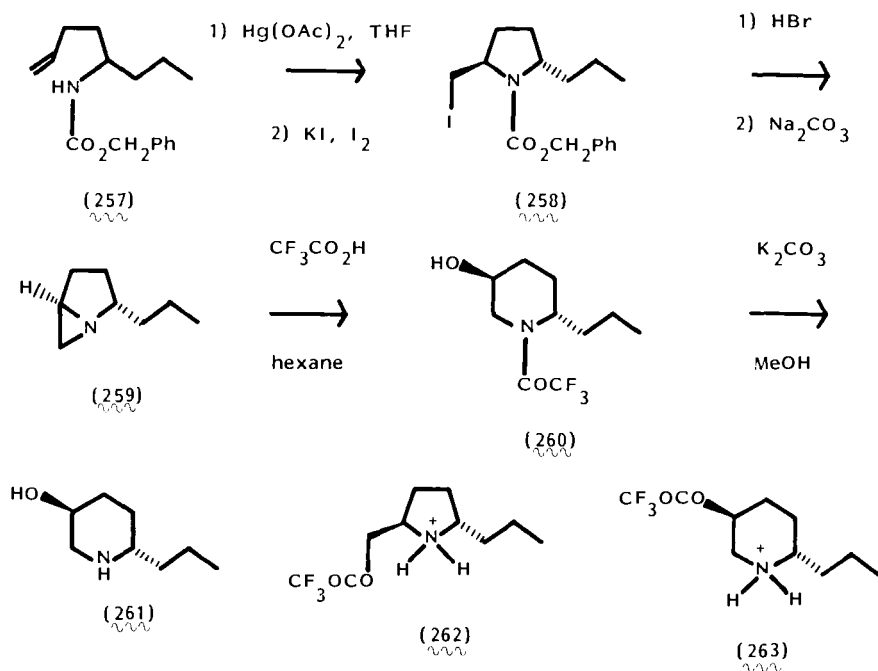
prepared from the olefinic carbamate **257** by employing intramolecular amidomercuration, followed by halogenation. The carbamate group of **258** was removed by treatment with hydrogen bromide in acetic acid, and the basic treatment of the resulting hydrobromide with sodium carbonate effected ring closure to the aziridine **259**. Although the ring-opening reaction of a bicyclic aziridine related to **259** has been reported⁸⁰ to proceed specifically to give a piperidine product upon treatment with electrophilic reagents, treatment of **259** with an excess of a protic acid afforded the corresponding pyrrolidine **262** as the major product under many of the reaction conditions. However, reaction of **259** with trifluoroacetic acid in hexane or toluene gave about a 3:7 ratio of **262** and **263**. These results demonstrated that the regiochemistry of ring opening of bicyclic aziridines is more complex than suggested by earlier reports⁸⁰ on these reactions. It has been concluded that the pyrrolidine product is the kinetic product of aziridine opening but that under conditions allowing equilibration the piperidine predominates as the thermodynamically favored product, as shown in Scheme 50.



SCHEME 50

Thus slow addition of 1 equiv of trifluoroacetic acid to **259** at room temperature furnished material that contains ~85% of the piperidine **260** according to NMR analysis. Finally, solvolysis of the trifluoroacetyl group of **260**, using potassium carbonate in methanol, gave (±)-pseudoconhydrine (**261**) (Scheme 51).

⁸⁰ D. E. Horning and J. M. Muchowski, *Can. J. Chem.* **52**, 1321 (1974); A. L. Logothetis, *J. Am. Chem. Soc.* **87**, 749 (1965).



SCHEME 51

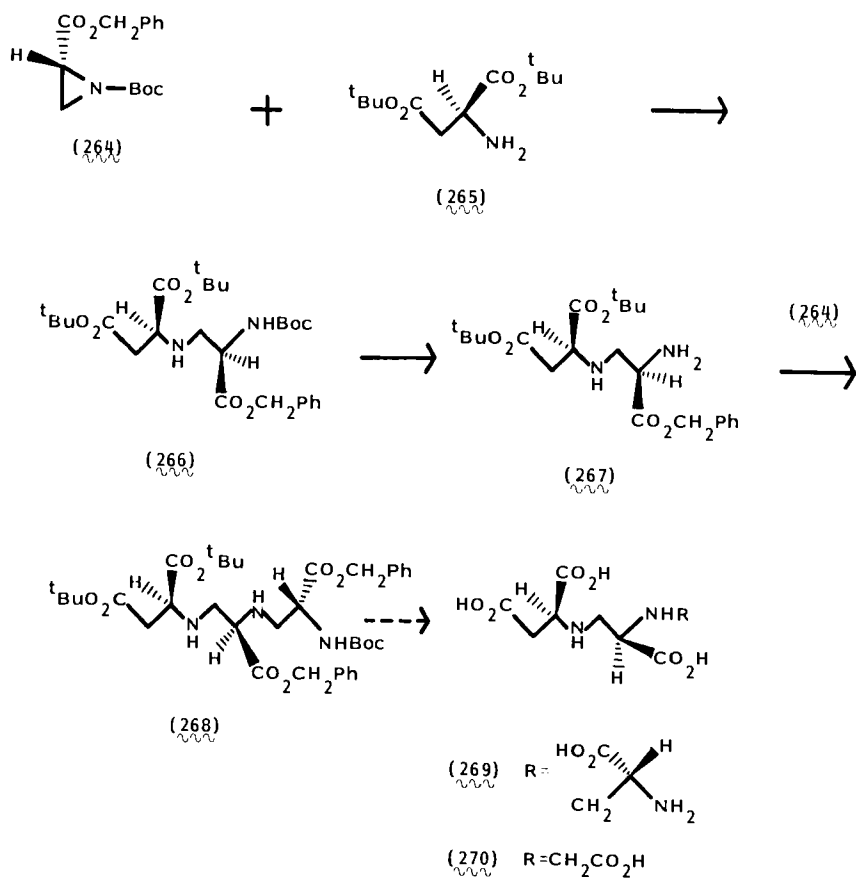
H. ASPERGILLOMARASMINE A AND B

Aspergillomarasmine A (269) and B (270) are toxic substances produced by *Aspergillus flavus-oryzae*. Synthesis of the amino acid 269 in an optically active form was attempted⁸¹ by employing a ring-opening reaction of the optically active aziridine 264, prepared from D-seline benzyl ester according to the known procedure,⁸² as a key reaction (Scheme 52). The aziridine 264, on treatment with the amine 265 derived from L-aspartic acid at 90°C for 12 h, afforded the ring-opened amine 266 in 84% yield. After deprotection of the Boc group on the primary amine with 90% formic acid, the resulting amine 267 was further treated with the aziridine 264 to give the protected aspergillomarasmine A (268), whose deprotection led to 269.

Moreover, the conversion of the amine 267 to aspergillomarasmine B (270) also seems possible.

⁸¹ S. Fushiya and S. Nozoe, *103rd Annu. Meet. Pharm. Soc. Jpn.*, 208 (1983).

⁸² T. Tanaka, K. Nakajima, and K. Okawa, *Bull. Chem. Soc. Jpn.* **53**, 1352 (1980).



SCHEME 52

Metallacycloalkanes and -alkenes

EKKEHARD LINDNER

*Institut für Anorganische Chemie, Universität Tübingen,
D-7400 Tübingen, Federal Republic of Germany*

I. Introduction	238
II. Metallacycloalkanes without and with Additional Heteroatoms	239
A. Methods for Syntheses	239
1. Cyclization of Bisalkene Complexes	239
2. Cationic Alkylation of Metal Lewis Bases	240
3. Anionic Alkylation of Metal Lewis Acids	244
4. Oxidative Addition of Substrates to Transition Metals	245
5. Addition of Alkenes to Metal Carbene Complexes	246
6. Reductive Cycloelimination of Bifunctionalized Metal Complexes	248
7. Cyclometalation Reactions	248
8. Reactions of Metal Complexes with Ylides	249
B. Structure and Physical Properties	250
1. X-Ray Crystallography	250
2. Spectroscopic Properties	251
C. Reactions of Metallacycloalkanes	253
1. Degradation Mechanisms	253
2. Metallacycloalkanes as Reactive Intermediates	254
3. Ring Contractions and Ring Expansions	259
4. Carbene Insertion Reactions	261
III. Metallacycloalkenes without and with Additional Heteroatoms	262
A. Methods for Syntheses	262
1. Cyclization of Bisalkyne Complexes	262
2. Cyclization of Alkyne/Alkene Complexes	263
3. Cyclization of Alkylthio Complexes with Alkynes	264
4. Photolysis of Metal Complexes in the Presence of Alkynes	265
5. Insertion of Alkynes into M—P or M—S Bonds	266
6. Oxidative Addition of Unsaturated Substrates to Transition Metals	268
7. Addition of Alkynes to Metal Carbyne Complexes	269
8. Reaction of Alkynes with Titanium—Aluminum—Alkyl Complexes	270
B. Structure and Physical Properties	270
1. X-Ray Crystallography	270
2. Spectroscopic Properties	272
C. Reactions of Metallacycloalkenes	273
1. Synthesis of Cycloalkenediones, Cyclopentenones, Cyclohexa- and Cyclopentadienones, Alkenes, and Dienes	273
2. Alkyne Metathesis	275
3. Cyclotrimerization of Alkynes	275

4. Cyclocotrimerization of Alkynes with Olefins, Nitriles, and Carbon Dioxide	276
5. Hetero P=S Analogous Cyclocotrimerization with Alkynes	278

I. Introduction

The chemistry of metal-containing heterocycles has developed enormously during the last few years. The present review therefore can only deal with compounds that have at least one metal-carbon σ bond. This study is focused on metallacycloalkanes and -alkenes without and with additional heteroatoms, which are of increasing interest because they occur in many transition metal-catalyzed organic syntheses as highly reactive intermediates.¹⁻⁴

In the case of reactions such as valence isomerization, metathesis reactions of alkenes and alkynes, oligomerization or cyclooligomerization of olefins, metallacycloalkanes are of special importance. Their catalytic efficiency depends on the ease of the M—C bond cleavage, which is the result of reductive elimination of the organic substrate or of β -hydrogen transfer. Also α - or β -C—C bond rupture has been reported. Heterocycles with an aliphatic carbon skeleton and a donor atom adjacent to the metal are suitable model compounds for the study of individual catalytic steps and structural properties.⁵⁻⁸ In connection with the activation of C—H bonds, cyclometallation has become a very general reaction and was reviewed in 1977.⁹

Not less attractive is the cyclooligomerization of alkynes, leading to benzene derivatives¹⁰ or cyclooctatetraene.¹ The cyclocotrimerization of alkynes proceeds via metallacycloprenes and -cyclopentadienes or, when alkenes are also involved, via metallacyclopentenes as intermediates. Cotrimerization of alkynes with nitriles affords pyridine derivatives.¹¹ Cyclocotrimerization of η^2 -thiophosphinites with alkynes in an analogous reaction leads to bicycloheptadienes, containing phosphorus and sulfur. A thiaphosphametallacyclopentadiene, which can be compared with its carbon analog, occurs as an intermediate.¹²

¹ G. Wilke, *Pure Appl. Chem.* **50**, 677 (1978).

² K. Itoh, *Fundam. Res. Homogeneous Catal.* **3**, 865 (1979).

³ R. J. Puddephatt, *Coord. Chem. Rev.* **33**, 149 (1980).

⁴ R. J. Puddephatt, *Comments Inorg. Chem.* **2**, 69 (1982).

⁵ E. Lindner and G. von Au, *J. Organomet. Chem.* **202**, 163 (1980).

⁶ E. Lindner, H.-J. Eberle, and S. Hoehne, *Chem. Ber.* **114**, 413 (1981).

⁷ E. Lindner, G. Funk, and S. Hoehne, *Chem. Ber.* **114**, 2465 (1981).

⁸ E. Lindner, G. Funk, and S. Hoehne, *Chem. Ber.* **114**, 3855 (1981).

⁹ M. I. Bruce, *Angew. Chem., Int. Ed. Engl.* **16**, 73 (1977).

¹⁰ R. G. Bergman, *Pure Appl. Chem.* **53**, 161 (1981).

¹¹ H. Bönemann, *Angew. Chem., Int. Ed. Engl.* **17**, 505 (1978).

¹² E. Lindner and C.-P. Krieg, *J. Organomet. Chem.* **269**, 65 (1984).

Methods for synthesis, structure and physical properties, and reactions of metallacycloalkanes and -alkenes will be described in this chapter.

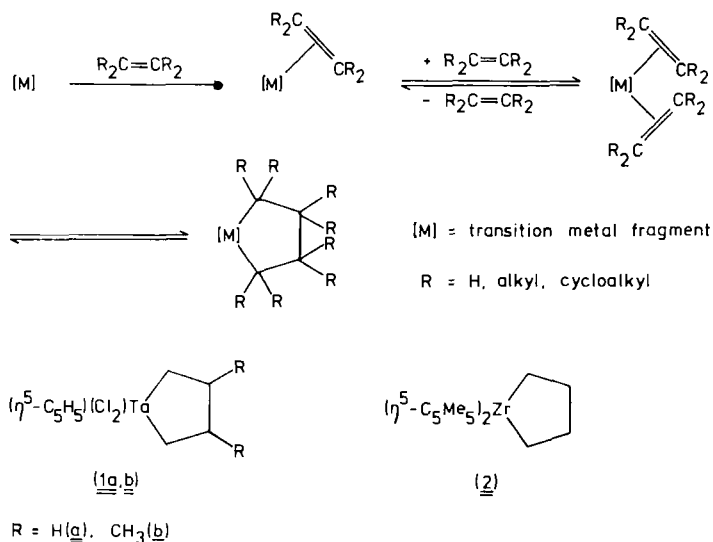
II. Metallacycloalkanes without and with Additional Heteroatoms

Metallacycloalkanes are obtained by several general methods; special methods are also known especially for metallacyclopentanes. When a donor atom like phosphorus or arsenic is present adjacent to the metal, the starting compounds must possess two functional centers. They can be generated in different ways. Without doubt metallacyclobutanes and -pentanes play a central role as important intermediates in numerous organometallic reactions.

A. METHODS FOR SYNTHESSES

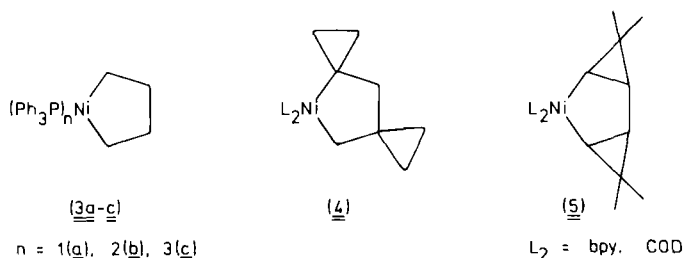
1. Cyclization of Bisalkene Complexes

Metallacycloalkanes are proven key intermediates in metal-catalyzed cycloadditions and cycloreversions of alkenes. The relationship of some d^6 iron metallacyclopentane derivatives with bis(olefin) complexes¹³ has been investigated theoretically. Scheme 1 shows a general route from bisalkene



SCHEME 1

¹³ A. Stockis and R. Hoffmann, *J. Am. Chem. Soc.* **102**, 2952 (1980).



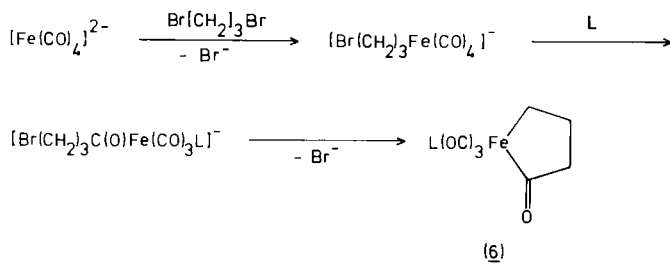
SCHEME 1 (continued)

complexes to metallacyclopentanes. Labeling experiments with nickel compounds have proved that the reaction is easily reversible.¹⁴ Formulas 1–5 show a few typical examples, which have been reported since 1976.^{15–27} Schrock *et al.*¹⁹ demonstrated that **1b** is an intermediate in the catalytic dimerization of propylene. Binger *et al.*^{23–27} have explored the catalytic cyclooligomerization of strained olefins such as methylenecyclopropane or dimethylcyclopropane. These reactions proceed via **4** and **5**.

2. Cationic Alkylation of Metal Lewis Bases

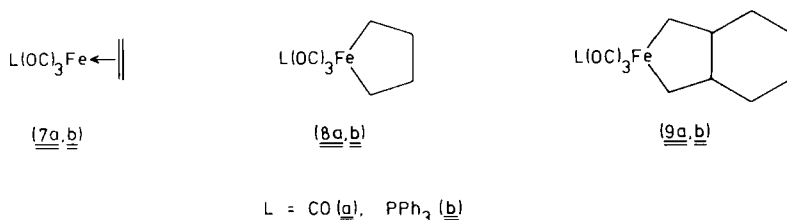
First attempts in preparing ferracycloalkanes by reaction of $[\text{Fe}(\text{CO})_4]^{2-}$ with 1,3-dibromopropane resulted in the formation of the 2-ferracyclopentanone **6** (Scheme 2).²⁸

- ¹⁴ R. H. Grubbs and A. Miyashita, *J. Am. Chem. Soc.* **100**, 1300, 7416 (1978); *J. C. S. Chem. Commun.*, 864 (1977).
- ¹⁵ J. X. McDermott, M. F. Wilson, and G. M. Whitesides, *J. Am. Chem. Soc.* **98**, 6529 (1976).
- ¹⁶ R. H. Grubbs, A. Miyashita, M. Liu, and P. Burk, *J. Am. Chem. Soc.* **99**, 3863 (1977); **100**, 2418 (1978).
- ¹⁷ J. M. Manriquez, D. R. McAlister, R. D. Sanner, and J. E. Bercaw, *J. Am. Chem. Soc.* **100**, 2716 (1978).
- ¹⁸ S. J. McLain, C. D. Wood, and R. R. Schrock, *J. Am. Chem. Soc.* **101**, 4558 (1979).
- ¹⁹ S. J. McLain, J. Sancho, and R. R. Schrock, *J. Am. Chem. Soc.* **101**, 5451 (1979); **102**, 5610 (1980).
- ²⁰ C. D. Wood, S. J. McLain, and R. R. Schrock, *J. Am. Chem. Soc.* **101**, 3210 (1979).
- ²¹ S. M. Rocklage, J. D. Fellman, G. A. Rupprecht, C. W. Messerle, and R. R. Schrock, *J. Am. Chem. Soc.* **103**, 1440 (1981).
- ²² J. D. Fellman, R. R. Schrock, and G. A. Rupprecht, *J. Am. Chem. Soc.* **103**, 5752 (1981).
- ²³ P. Binger, M. Cetinkaya, M. J. Doyle, A. Germer, and U. Schuchardt, *Fundam. Res. Homogeneous Catal.* **3**, 271 (1979).
- ²⁴ P. Binger, H. M. Büch, R. Benn, and R. Mynott, *Angew. Chem., Int. Ed. Engl.* **21**, 62 (1982).
- ²⁵ P. Binger, M. J. Doyle, and R. Benn, *Chem. Ber.* **116**, 1 (1983).
- ²⁶ P. Binger, A. Brinkmann, and P. Wedemann, *Chem. Ber.* **116**, 2920 (1983).
- ²⁷ P. Binger, T. R. Martin, R. Benn, A. Rufinska, and G. Schroth, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **39B**, 993 (1984).
- ²⁸ Y. Watanabe, T. Mitsudo, M. Yamashita, M. Tanaka, and Y. Takegami, *Chem. Lett.*, 475 (1973).



SCHEME 2

Synthesis of ferracycloalkanes became possible only when the corresponding alkanediylbis(trifluoromethanesulfonates)²⁹ with the excellent leaving group $\text{CF}_3\text{SO}_2\text{O}^-$ were available. In these bistriflates two carbenium-like carbon atoms are present, a precondition for the nucleophilic attack of an appropriate metal Lewis base to form a metallacyclic compound. The action of such bistriflates on $[\text{Fe}(\text{CO})_3\text{L}]^{2-}$ yields the ferracycloalkanes **7–9**.^{30,31}



Several oxaphosphamanganacycloalkanes (**10a–d**)^{6,32,33} and -cycloalkanones (**11**)³⁴ (Scheme 3) were obtained by the same method, starting from the bifunctionalized anions $[(\text{OC})_4\text{MnPR}_2\text{O}]^{2-}$. Alternatively (Scheme 4), oxaphospharhenacycloalkanes^{5,35,36} (**12** and **13**) can also be synthesized by heterolytic cleavage of the Re—Re bond in the anions $[(\text{OC})_4\text{RePR}_2\text{O}]_2^{2-}$ with electrophiles.

Three-membered phosphametallacyclopropanes of the type **14**³⁷ and

²⁹ E. Lindner, G. von Au, and H.-J. Eberle, *Chem. Ber.* **114**, 810 (1981).

³⁰ E. Lindner, E. Schauss, W. Hiller, and R. Fawzi, *Angew. Chem., Int. Ed. Engl.* **23**, 711 (1984).

³¹ E. Lindner, E. Schauss, W. Hiller, and R. Fawzi, *Chem. Ber.* **118**, 3915 (1985).

³² E. Lindner and H.-J. Eberle, *Angew. Chem., Int. Ed. Engl.* **19**, 73 (1980).

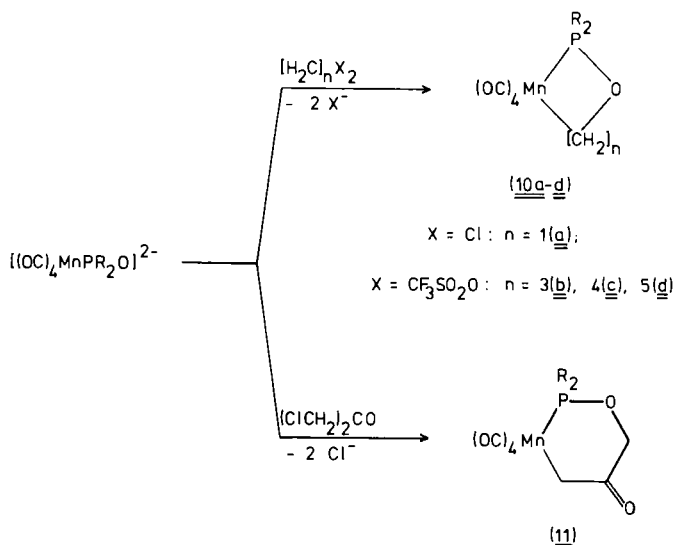
³³ E. Lindner and H.-J. Eberle, *J. Organomet. Chem.* **191**, 143 (1980).

³⁴ E. Lindner, K. A. Starz, N. Pauls, and W. Winter, *Chem. Ber.* **116**, 1070 (1983).

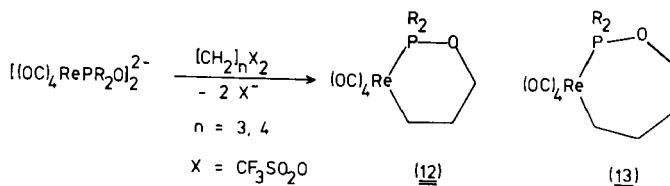
³⁵ E. Lindner and G. von Au, *Angew. Chem., Int. Ed. Engl.* **19**, 824 (1980).

³⁶ E. Lindner and G. von Au, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **35B**, 1104 (1980).

³⁷ E. Lindner, K. A. Starz, H.-J. Eberle, and W. Hiller, *Chem. Ber.* **116**, 1209 (1983).

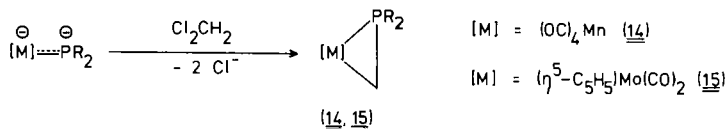


SCHEME 3



SCHEME 4

15³⁸ (Scheme 5) are accessible by nucleophilic elimination–cycloaddition of geminal dichlorides with the anions $[(\text{OC})_4\text{MnPPh}_2]^{2-}$ and $[(\eta^5\text{-C}_5\text{H}_5)\text{Mo}(\text{CO})_2\text{PPh}_2]^{2-}$, respectively.



SCHEME 5

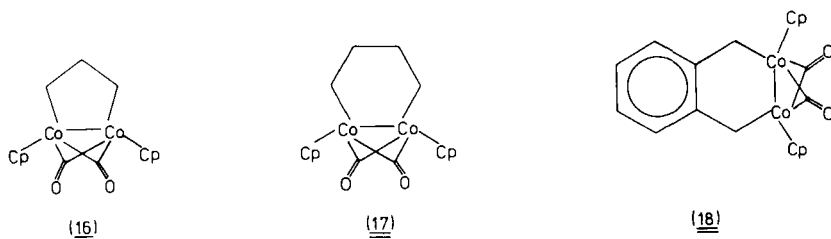
For the preparation of sulfur-containing phosphamanganacyclohexanes, 1,3-dibromopropane can be used.³⁹

To investigate the stereochemistry of metallacycles, a series of dicobaltacycloalkanes with cobalt–cobalt bonds were described by Bergman

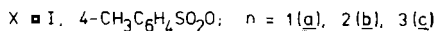
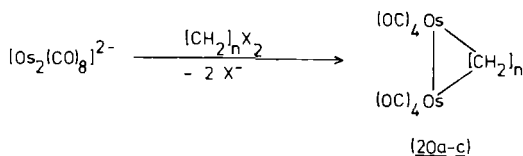
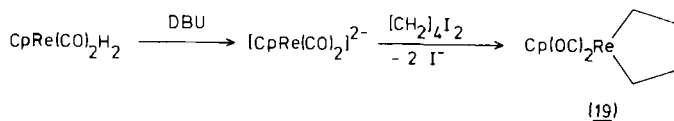
³⁸ E. Lindner, E. U. Küster, W. Hiller, and R. Fawzi, *Chem. Ber.* **117**, 127 (1984).

³⁹ E. Lindner, G. von Au, and H.-J. Eberle, *J. Organomet. Chem.* **204**, 93 (1981).

*et al.*⁴⁰⁻⁴⁵ The cyclization is achieved by reaction of the anionic radical $[(\eta^5\text{-C}_5\text{H}_5)\text{Co}(\mu_2\text{-CO})_2\text{-Co}(\eta^5\text{-C}_5\text{H}_5)]^-$ with $\text{I}-[\text{CH}_2]_n\text{-I}$.



Abstraction of H^+ from $\text{CpRe}(\text{CO})_2\text{H}_2$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) with the base DBU (Scheme 6) affords the anion $[\text{CpRe}(\text{CO})_2]^{2-}$, which reacts with $\text{I}-[\text{CH}_2]_4\text{-I}$ to give **19**.^{46,47}



SCHEME 6

For synthesis of the diosmacyclopentane **20c**, the use of $\text{I}-[\text{CH}_2]_3\text{-I}$ gave reasonable results, but for the smaller rings **20a,b** the use of $\text{CH}_2(\text{OTos})_2$ and $\text{TosOCH}_2\text{CH}_2\text{OTos}$ proved more satisfactory (Scheme 6).⁴⁸

⁴⁰ K. H. Theopold and R. G. Bergman, *J. Am. Chem. Soc.* **102**, 5694 (1980).

⁴¹ W. H. Hersh and R. G. Bergman, *J. Am. Chem. Soc.* **103**, 6992 (1981).

⁴² K. H. Theopold and R. G. Bergman, *Organometallics* **1**, 1571 (1982).

⁴³ K. H. Theopold, P. N. Becker, and R. G. Bergman, *J. Am. Chem. Soc.* **104**, 5250 (1982).

⁴⁴ W. H. Hersh, F. J. Hollander, and R. G. Bergman, *J. Am. Chem. Soc.* **105**, 5834 (1983).

⁴⁵ G. K. Yang and R. G. Bergman, *J. Am. Chem. Soc.* **105**, 6045 (1983).

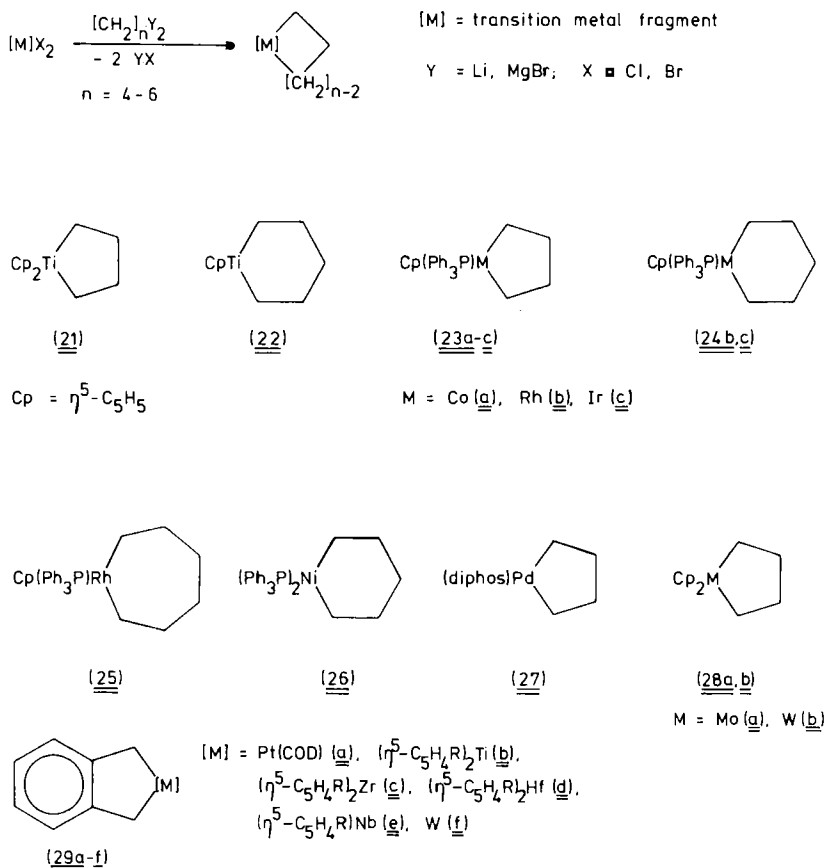
⁴⁶ G. K. Yang and R. G. Bergman, *J. Am. Chem. Soc.* **105**, 6500 (1983).

⁴⁷ G. K. Yang and R. G. Bergman, *Organometallics* **4**, 129 (1985).

⁴⁸ K. M. Motyl, J. R. Norton, C. K. Schauer, and O. P. Anderson, *J. Am. Chem. Soc.* **104**, 7325 (1982).

3. Anionic Alkylation of Metal Lewis Acids

A very good method for the synthesis of metallacycles with two metal-carbon σ bonds is the reaction of dihalogenometal complexes with α,ω -dilithio- or di-Grignard-alkanes (Scheme 7). According to this procedure, metallacyclobutanes,⁴⁹⁻⁵¹ -pentanes, -hexanes, and -heptanes of tita-



SCHEME 7

⁴⁹ J. W. Bruin, G. Schat, O. S. Akkerman, and F. Bickelhaupt, *Tetrahedron Lett.* **24**, 3935 (1983).

⁵⁰ B. J. J. van de Heistee, G. Schat, O. S. Akkerman, and F. Bickelhaupt, *Tetrahedron Lett.* **25**, 5191 (1984).

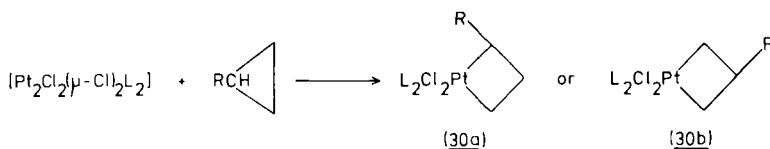
⁵¹ J. W. F. L. Seetz, B. J. J. van de Heistee, G. Schat, O. S. Akkerman, and F. Bickelhaupt, *J. Organomet. Chem.* **275**, 173 (1984).

mium,^{15,52} cobalt,⁵³ rhodium,⁵³⁻⁵⁵ iridium,⁵³ palladium,⁵⁶ nickel,^{14,57} molybdenum,⁵⁸ and tungsten⁵⁸ have been prepared. Typical examples are compounds **21** – **28** (Scheme 7).

O-Xylidene complexes of type **29** are obtained by the same route.⁵⁹⁻⁶²

4. Oxidative Addition of Substrates to Transition Metals

The oxidative addition of methylene- or allylidenecyclopropane to nickel(0) or palladium(0) can also lead to the formation of six-, seven-, and nine-membered metallacycles of nickel²³⁻²⁷ and palladium.⁶³ Various substituted platinacyclobutanes (**30**) were obtained by oxidative addition of cyclopropanes to the complexes $[\text{Cl}_2\text{PtL}]_2$ (Scheme 8).^{3,4,64-69}

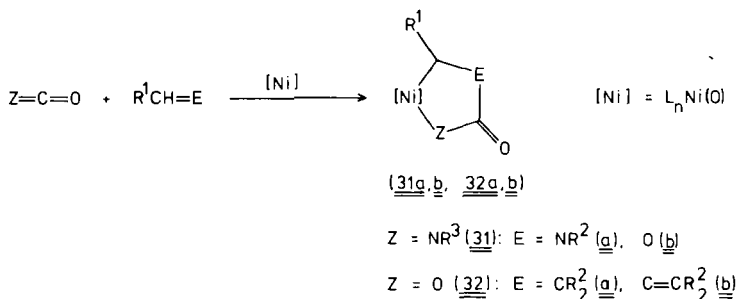


SCHEME 8

- ⁵² J. X. McDermott and G. M. Whitesides, *J. Am. Chem. Soc.* **96**, 947 (1974).
- ⁵³ P. Diversi, G. Ingrosso, A. Lucherini, W. Porzio, and M. Zocchi, *Inorg. Chem.* **19**, 3590 (1980); *J. C. S. Chem. Commun.*, 811 (1977).
- ⁵⁴ P. Diversi, G. Ingrosso, and A. Lucherini, *J. C. S. Chem. Commun.*, 52 (1977).
- ⁵⁵ P. Diversi, G. Ingrosso, A. Lucherini, P. Martinelli, M. Benetti, and S. Pucci, *J. Organomet. Chem.* **165**, 253 (1979).
- ⁵⁶ P. Diversi, G. Ingrosso, and A. Lucherini, *J. C. S. Chem. Commun.*, 735 (1978).
- ⁵⁷ R. H. Grubbs and A. Miyashita, *J. Am. Chem. Soc.* **100**, 7418 (1978).
- ⁵⁸ P. Diversi, G. Ingrosso, A. Lucherini, W. Porzio, and M. Zocchi, *J. C. S. Dalton Trans.*, 967 (1983).
- ⁵⁹ M. F. Lappert, T. R. Martin, C. L. Raston, B. W. Skelton, and A. H. White, *J. C. S. Dalton Trans.*, 1959 (1982).
- ⁶⁰ G. S. Bristow, M. F. Lappert, T. R. Martin, J. L. Atwood, and W. F. Hunter, *J. C. S. Dalton Trans.*, 399 (1984).
- ⁶¹ M. F. Lappert, C. L. Raston, G. L. Rowbottom, B. W. Skelton, and A. H. White, *J. C. S. Dalton Trans.*, 883 (1984).
- ⁶² M. F. Lappert, C. L. Raston, B. W. Skelton, and A. H. White, *J. C. S. Dalton Trans.*, 893 (1984).
- ⁶³ H. M. Büch, P. Binger, R. Benn, C. Krüger, and A. Rufinska, *Angew. Chem., Int. Ed. Engl.* **22**, 774 (1983).
- ⁶⁴ R. J. Al-Essa, R. Puddephatt, M. A. Quyser, and C. F. H. Tipper, *Inorg. Chim. Acta* **34**, L187 (1979); *J. Am. Chem. Soc.* **101**, 364 (1979).
- ⁶⁵ R. J. Al-Essa, R. J. Puddephatt, D. C. L. Perkins, M. C. Rendle, and C. F. H. Tipper, *J. C. S. Dalton Trans.*, 1738 (1981).
- ⁶⁶ T. H. Johnson, *J. Org. Chem.* **44**, 1356 (1979).
- ⁶⁷ T. H. Johnson, T. F. Baldwin, and K. C. Klein, *Tetrahedron Lett.* **20**, 1191 (1979).
- ⁶⁸ B. M. Cushman, S. E. Earnest, and D. B. Brown, *J. Organomet. Chem.* **159**, 431 (1978).
- ⁶⁹ B. M. Cushman and D. B. Brown, *Inorg. Chem.* **20**, 2490 (1981).

"Ligand-free" platinum compounds are excellent starting materials for access to platinacycloalkanes with different ring size.⁷⁰

Unsaturated substrates can be coupled with heterocumulenes on nickel(0) complexes to give the nickelaheterocycles **31** and **32**. In this context it is possible to treat alkenes with CO₂,⁷¹ 1,3-dienes,^{72,73} and 1,2-dienes,⁷⁴ and isocyanates with imines⁷⁵ and aldehydes,⁷⁶ respectively (Scheme 9). Com-



SCHEME 9

pounds of type **31** or **32** can also be obtained by oxidative addition of α,β -unsaturated amides,⁷⁷ acids,⁷⁸ or cyclic carboxylic anhydrides⁷⁹ to Ni(0) complexes.

An interesting variant⁸⁰ for synthesizing rhoda- or platinacyclopentanes (**33** and **34**, respectively) is the oxidative addition of a C—Cl bond to rhodium or platinum (Scheme 10).

5. Addition of Alkenes to Metal Carbene Complexes

Between carbene complexes and alkenes on the one side and metallacyclobutanes on the other, there exists an equilibrium.^{18-22,57,81,82} This can be

⁷⁰ F. G. A. Stone, *Acc. Chem. Res.* **14**, 318 (1981).

⁷¹ H. Hoberg and D. Schaefer, *J. Organomet. Chem.* **236**, C28 (1982); **251**, C51 (1983).

⁷² H. Hoberg, D. Schaefer, and B. W. Oster, *J. Organomet. Chem.* **266**, 313 (1984).

⁷³ D. Walther and E. Dinjus, *Z. Chem.* **22**, 228 (1982).

⁷⁴ H. Hoberg and B. W. Oster, *J. Organomet. Chem.* **266**, 321 (1984).

⁷⁵ H. Hoberg and K. Sümmermann, *J. Organomet. Chem.* **253**, 383 (1983).

⁷⁶ H. Hoberg and K. Sümmermann, *J. Organomet. Chem.* **264**, 379 (1984); *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **39B**, 1032 (1984).

⁷⁷ T. Yamamoto, K. Igarashi, S. Komiya, and A. Yamamoto, *J. Am. Chem. Soc.* **102**, 7448 (1980).

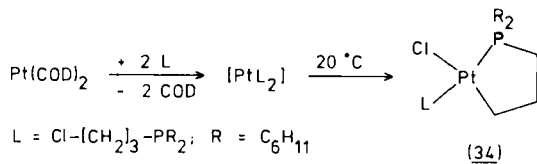
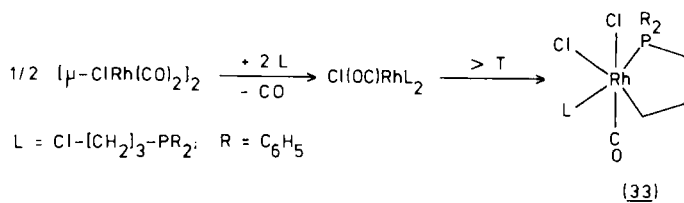
⁷⁸ K. Sano, T. Yamamoto, and A. Yamamoto, *Chem. Lett.*, 695 (1982).

⁷⁹ K. Sano, T. Yamamoto, and A. Yamamoto, *Chem. Lett.*, 115 (1983).

⁸⁰ E. Lindner, F. Bouachir, R. Fawzi, and D. Hübner, *J. Organomet. Chem.* **235**, 345 (1982).

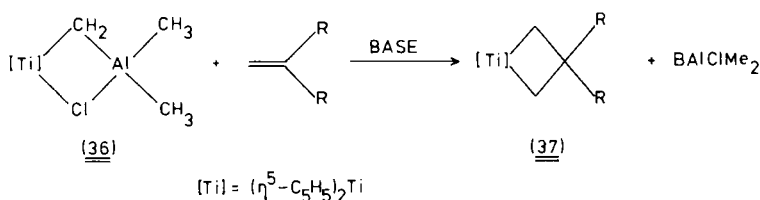
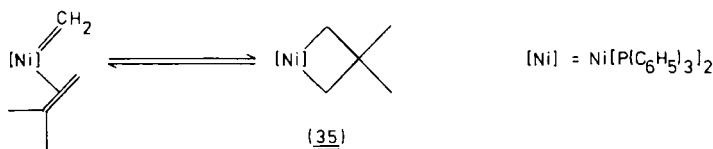
⁸¹ R. H. Grubbs, *Prog. Inorg. Chem.* **24**, 1 (1978).

⁸² R. H. Grubbs and A. Miyashita, *Fundam. Res. Homogeneous Catal.* **3**, 51 (1979).



SCHEME 10

used to prepare metallacyclobutanes as depicted in **35** (Scheme 11). A precursor for a metal carbene complex is Tebbe's metathesis catalyst (36) (Scheme 11).⁸³ Titanacyclobutanes (37) were found as intermediates in olefin metathesis by Grubbs *et al.*⁸⁴⁻⁸⁶



SCHEME 11

⁸³ F. N. Tebbe, G. W. Parshall, and D. W. Ovenall, *J. Am. Chem. Soc.* **101**, 5074 (1979).

⁸⁴ T. R. Howard, J. B. Lee, and R. H. Grubbs, *J. Am. Chem. Soc.* **102**, 6876 (1980).

⁸⁵ J. B. Lee, G. J. Gajda, W. P. Schaefer, T. R. Howard, T. Ikariya, D. A. Straus, and R. H. Grubbs, *J. Am. Chem. Soc.* **103**, 7358 (1981).

⁸⁶ J. B. Lee, K. C. Ott, and R. H. Grubbs, *J. Am. Chem. Soc.* **104**, 7491 (1982).

6. Reductive Cycloelimination of Bifunctionalized Metal Complexes

For various ring sizes of phospho- and arsametallacycloalkanes, reductive cycloelimination with sodium amalgam gave the best results.⁸⁷ As starting materials, bifunctionalized metal complexes are employed, which are accessible by substituting CO by the ligand $\text{ER}_2\text{—}[\text{CH}_2]_n\text{—X}$,^{7,8,88,89} in carbonyl metal compounds with at least one metal–halogen bond. Whereas three- (14) and eight-membered metallacycles of this type can be obtained only in traces, the yields of four- to seven-membered rings vary between 15 and 95%. According to Scheme 12, metallacycloalkanes of molybdenum (38),³⁸ tungsten (39),^{38,90} manganese (40),^{7,8,89,91,92} rhenium (41),^{7,89} iron (42),⁹⁰ cobalt (43),⁹³ and nickel (44),^{90,94} with different ring sizes, are described. The reason for the failure to synthesize phosphametallacyclooctanes 38e–44e can be traced back to the low probability of the direct vicinity of both halogen atoms X in the educts $[\text{M}](\text{X})\text{—ER}_2\text{—}[\text{CH}_2]_n\text{—X}$, which is necessary for the reductive cycloelimination. Thermodynamic aspects are not of importance.

The unstable five-membered oxaphosphamanganacyclopentanes 10e⁹⁵ are isolated only by reductive cycloelimination of $(\text{OC})_4\text{BrMnPPh}_2\text{O—CHR}^1\text{—CHR}^2\text{Cl}$ (Scheme 12) at 0°C. The influence of R¹ and R² (CH₃ or H) on the decomposition of 10e has been studied kinetically. Introduction of a phosphane into the ligand sphere of manganese, having a cis position with respect to the ring, results in an increasing lability of 10e.⁹⁶ A molybdenum metallacycle could be synthesized similarly.⁹⁷

7. Cyclometalation Reactions

When a transition metal complex is present, having a ligand that is metalated intramolecularly (activation of a C—H bond), a metallacycle with a metal–carbon σ bond is formed (Scheme 13). Metalations of phenyl-substi-

⁸⁷ M. Mickiewicz, K. P. Wainwright, and S. B. Wild, *J. C. S. Dalton Trans.*, 262 (1976); P. D. Brotherton, C. L. Raston, A. H. White, and S. B. Wild, *ibid.*, 1193.

⁸⁸ S. O. Grim and S. C. Barth, *J. Organomet. Chem.* **94**, 327 (1975).

⁸⁹ E. Lindner, F. Zinsser, W. Hiller, and R. Fawzi, *J. Organomet. Chem.* **288**, 317 (1985).

⁹⁰ E. Lindner, G. Funk, and F. Bouachir, *Chem. Ber.* **114**, 2653 (1981).

⁹¹ E. Lindner, G. Funk, and S. Hoehne, *Angew. Chem., Int. Ed. Engl.* **18**, 535 (1979).

⁹² E. Lindner, K. A. Starz, and S. Hoehne, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **37B**, 1301 (1982).

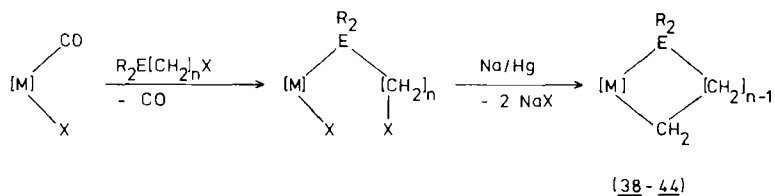
⁹³ E. Lindner and R. Fawzi, unpublished results.

⁹⁴ E. Lindner, F. Bouachir, and W. Hiller, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **37B**, 1146 (1982).

⁹⁵ E. Lindner and A. Brösamle, *Chem. Ber.* **117**, 2730 (1984).

⁹⁶ E. Lindner and A. Brösamle, *Chem. Ber.* **118**, 2134 (1985).

⁹⁷ E. Lindner and A. Brösamle, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **39B**, 535 (1984).

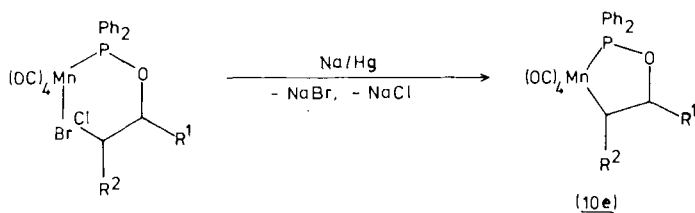


E = P, As; R = CH₃, C₆H₅; X = Br, I; [M] = (η⁵-C₅H₅)M(CO)₂

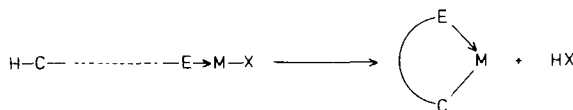
[M = Mo (38), W (39)], M(CO)₄ [M = Mn (40), Re (41)],

(η⁵-C₅H₅)FeCO (42), Co(CO)₃ (43), (η⁵-C₅H₅)Ni (44);

n = 2 (a), 3 (b), 4 (c), 5 (d), 6 (e)



SCHEME 12



SCHEME 13

tuted⁹⁸ ligands were mostly described and denoted as ortho metalations. An enormous number of papers have been published and they are reviewed elsewhere.⁹

8. Reactions of Metal Complexes with Ylides

Since 1970 Schmidbaur reported the preparation and properties of a new class of ylide complexes, among which are a large number of metal-contain-

⁹⁸ B. T. Huie, C. B. Knobler, R. J. McKinney, and H. D. Kaesz, *J. Am. Chem. Soc.* **99**, 7862 (1977).

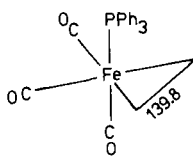
ing heterocycles with metal-carbon σ bonds. These results have been reviewed several times.⁹⁹⁻¹⁰²

B. STRUCTURE AND PHYSICAL PROPERTIES

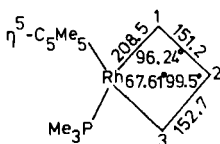
Unsubstituted metallacycloalkanes ordinarily are volatile, thermally labile, air sensitive, and easily soluble in nonpolar solvents such as saturated hydrocarbons. Their structural and physical properties therefore usually require study at low temperatures.

1. X-Ray Crystallography

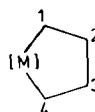
Because of their instability, few crystallographic studies have been carried out on metallacycloalkanes. An example of a three-membered ring is the iron compound **7b**. X-Ray structural analysis confirms the equatorial arrangement of ethene.^{30,31} The short C—C bond distance of 139.8 pm proves **7b** to be more a π complex than a ferracyclopropane. The rhodacyclobutane **45**¹⁰³ is essentially planar and symmetrical about the Rh—C-2 axis.



(7b)



(45)



(1a, with $\eta^5\text{-C}_5\text{Me}_5$.

8b, 23a-c, 28a)

Depending on steric factors and the coordination sphere of the metal, metallacyclopentanes occur in three structural isomers. They can have an open-envelope conformation¹⁰⁴ (compound **1a**¹⁰⁵), in which the carbon frame C-1—C-4 is close to being planar, or a twisted open-envelope structure (compound **19**¹⁰⁶). A third possibility is a puckered conformation (com-

⁹⁹ H. Schmidbaur, *Angew. Chem., Int. Ed. Engl.* **15**, 728 (1976).

¹⁰⁰ H. Schmidbaur, *Angew. Chem., Int. Ed. Engl.* **22**, 907 (1983).

¹⁰¹ H. Schmidbaur and K. C. Dash, *Adv. Inorg. Chem. Radiochem.* **25**, 239 (1982).

¹⁰² H. Schmidbaur, *Acc. Chem. Res.* **8**, 62 (1975).

¹⁰³ R. A. Periana and R. G. Bergman, *J. Am. Chem. Soc.* **106**, 7272 (1984).

¹⁰⁴ Y. Wakatsuki, T. Sakurai, and H. Yamazaki, *J. C. S. Dalton Trans.*, 1923 (1982).

¹⁰⁵ M. R. Churchill and W. J. Youngs, *Inorg. Chem.* **19**, 3106 (1980).

¹⁰⁶ G. K. Yang and R. G. Bergman, *Organometallics* **4**, 129 (1985).

pound **8b**^{30,31}). In the last two cases one must be careful in determining structures: C-2—C-3 bond lengths can be obtained that are too short.^{53,58} Because of conformational chirality, C-2 and C-3 in **8b**^{30,31} and **19**¹⁰⁶ are disordered. This was taken into consideration in calculating the structure by introducing split positions. The C-2—C-3 distance corresponds to a single bond (**8b**: 152 pm; **19**: 149 pm). The dicobaltacyclopentane **16** has an envelope conformation.⁴² The X-ray structure has been published for the largest hitherto known metallacycle, a nine-membered palladacyclononane.⁶³

Because of their thermodynamic stability, the metallacycles **10–15** and **38–44** with a donor atom adjacent to the metal are suitable models for the study of structural and physical properties. With the exception of **40a**⁷ in the series of manganacycloalkanes $(OC)_4MnPPH_2[CH_2]_n$ (**14**,³⁷ **40b–d**^{7,8,89,91}) all structures are known (Table I). The bond distances of **40d**⁸⁹ are in good agreement with those of the five- and six-membered manganacycles^{7,8} but are different from the three-³⁷ and four-membered⁷ homologs, the P—C bond lengths of which are obviously shorter. The C—C distance in the four-membered ring $(OC)_4RePPH_2CH_2CH_2$ (**41a**)⁷ is unusually long at 168 pm. The manganacyclopropane **14** occupies an exceptional position in every respect.³⁷ The short P—C distance reminds of the structure of the ethylene complex of iron **7b**.^{30,31} Compound **41a**⁷ has a planar, **40b**^{7,91} an envelope, **40c**⁸ a distorted chair, and **40d**⁸⁹ a boat conformation.

2. Spectroscopic Properties

Metallacycloalkanes can be characterized efficiently by their NMR and mass spectra and, if they have functional groups, also by their IR spectra.

a. *Infrared Spectra.* Metallacycloalkanes with functional groups such as carbon monoxide in the coordination sphere of the metal, are appropriate

TABLE I
COMPARISON OF SOME BOND LENGTHS AND ANGLES IN THE HETEROCYCLES
 $(OC)_4MPPH_2-[CH_2]_n$ (**14**, **41a**, **40b–d**; $n = 1-5$)

Compound	Bond lengths (pm)			Bond angles (°)		References
	M—P	M—C	P—C	P—M—C	M—P—C	
14 ($n = 1$)	222.2	217.8	175.3	46.9	65.2	37
41a ($n = 2$)	—	—	176.7	66.5	91.8	7
40b ($n = 3$)	229.5	216.1	182.1	81.7	105.9	7,91
40c ($n = 4$)	230.3	222.2	182.8	90.8	114.2	8
40d ($n = 5$)	233.1	220.2	182.8	86.9	116.4	89

for IR spectroscopic investigations. The spectra of the ferracycloalkanes **7a–9a** and **7b–9b** show four and three sharp CO absorptions, respectively, near the $5\text{ }\mu\text{m}$ region.^{30,31} In the complete series of oxaphospha- or phosphamanganacycloalkanes **10a–e**,^{6,32,33,95} **14**,³⁷ and **40a–e**,^{7,8,89} four indicative CO bands can be observed in the $5\text{-}\mu\text{m}$ region (Table II), showing a trend to shorter wavelengths with larger ring size.

b. *¹H-NMR Spectra.* The ¹H-NMR spectra of most metallacycloalkanes represent only unresolved multiplets.^{5–8,18,30,31,53–56,58} The multiplet that occurs at highest field usually can be traced back to the methylene protons adjacent to the metal. Only in the spectra of metallacycloalkanes containing an ethylene group, such as **10e**,⁹⁵ **40a**, or **41a**,⁷ are two doublets of triplets observed because of mutual and additional ³¹P coupling of the metal and CH₂ protons adjacent to phosphorus.

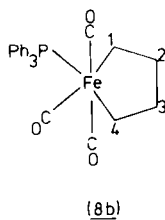
The spectrum of **14** (in CDCl₃, relative to TMS) shows a singlet at δ 0.5.³⁷ The methylene protons of **15**³⁸ at 40°C (in CD₂Cl₂) give rise to a doublet because of ³¹P coupling. At –80°C the protons become diastereotopic and are coupled with each other. From this dynamic behavior the free activation energy can be calculated, $\Delta G^\ddagger = 53.9\text{ kJ/mol}$. Coalescence is observed at –10°C.

c. *¹³C-NMR Spectra.* From the well-resolved ¹³C-NMR spectra much more information is gathered. In the spectra of metallacyclopentanes, the lower field signal is due to C_α and the higher to C_β.^{30,31,58} In contrast to the ferracyclopentane **8a** [δ 22.1 (s, C_α), 36.6 (s, C_β); CDCl₃, relative to TMS,

TABLE II
CO ABSORPTIONS^a IN THE IR SPECTRA OF THE MANGANACYCLOALKANES
(OC)₄MnPPh₂O—[CH₂]_n (**10a–c,e**) AND (OC)₄MnPPh₂—[CH₂]_n (**14**, **40a–d**)
(*n*-HEXANE)

<i>n</i> = 1	<i>n</i> = 2	<i>n</i> = 3	<i>n</i> = 4	<i>n</i> = 5	References
10a	10e	10b	10c		6,32,33,95
2070 m	2067 m	2061 m	2059 m		
1996 m–s	1998 m–s	1994 s	1995 s		
1985 vs	1983 vs	1977 vs	1973 vs		
1961 s	1949 s	1946 s	1943 s		
14	40a	40b	40c	40d	7,8,37,89
2062 m	2058 m–s	2058 m–s	2056 m–s	2056 s	
1989 m	1987 s	1987 s	1987 s	1984 s	
1975 vs	1970 vs	1971 vs	1970 vs	1968 vs	
1952 s–vs	1947 s–vs	1942 s–vs	1943 s–vs	1943 s–vs	

^a In cm^{–1}.



20.115 MHz], because of the PPh_3 ligand, **8b** gives rise to four signals, which are split into doublets for C-1, C-3, and C-4. The larger coupling constant is ascribed to the *trans*-C-4—Fe—P group [δ 21.0 (d, $^2J_{\text{PC}} = 10.2$ Hz; C-4), 26.8 (d, $^2J_{\text{PC}} = 5.1$ Hz; C-1), 35.0 (d, $^3J_{\text{PC}} = 8.9$ Hz; C-3), 37.3 (s, C-2); CDCl_3 , relative to TMS, 20.115 HMz]. The assignment of the signals is corroborated by studies of **8a,b** in which the β positions were labeled by deuterium.^{30,31} The spectrum of the “ferracyclopropane” **7b**^{30,31} reveals a singlet for the ethylene protons at δ 37.4. In comparison with **7b**, the three-membered heterocycle $(\text{OC})_4\text{MnPPH}_2\text{CH}_2$ (**14**) shows a singlet at $\delta - 16.6$ ³⁷ for the methylene C atom, which resembles an ylide.¹⁰⁷

d. *Mass Spectra.* Metallacycloalkanes are volatile compounds, and, if they are not too unstable, their composition can be studied by mass spectra. Heterocycles containing CO ligands in the coordination sphere of the metal generally first eliminate these molecules before the ring skeleton is fragmented.^{5-8,30-39,89-97}

C. REACTIONS OF METALLACYCLOALKANES

The reactivity of metallacycloalkanes is quite different from that of their carbon analogs because the metal exerts a remarkable influence on the adjacent carbon and hydrogen atoms. For this reason metallacycloalkanes occur as highly reactive intermediates in many transition metal-catalyzed organic syntheses, typical examples of which are given in the following sections.

1. Degradation Mechanisms

The catalytic efficiency of metallacycloalkanes depends on their stability. Of special importance for the degradation mechanisms are β -hydrogen

¹⁰⁷ H. Schmidbaur, *Adv. Organomet. Chem.* **14**, 205 (1976).

transfer,^{108,109} reductive elimination of the organic substrate,¹¹⁰ and α - or β -C—C cleavage.^{16,57} A typical example of a reductive elimination of a carbon-carbon bond from bis(trialkylphosphane)-3,3-dimethylplatina-cyclobutanes, producing 1,1-dimethylcyclopropane, was demonstrated by Whitesides and DiCosimo.¹¹¹

The lower stability of σ -alkyl complexes and metallacycloalkanes with larger ring size, which is in contrast to metallacyclopentanes and -hexanes, can be traced to a sterically favorable transition state for β -H transfer, which requires an M—C—C—H dihedral angle of about 0° .^{108,112} If in the case of titanacyclopentanes a similar transition state with an M—C—C—C dihedral angle of about 0° is present, a C—C bond cleavage takes place.⁵² By a β -H transfer and subsequent ring contraction, ferra-^{30,31} and tantalacyclopentanes yield different hydrocarbons and methylene complexes.^{18,19,113,114}

According to Grubbs *et al.* the degradation of nickela- and titanacyclopentane derivatives depends on the coordination number of the metal.¹⁶ When the coordination number is 5, nickelacyclopentanes undergo β -C—C rupture; the corresponding hexanes, however, prefer α -C—C bond cleavage.⁵⁷ The relationship of geometry and coordination number to the degradation pathways of nickelacyclopentanes to cyclobutane or ethylene have been explored and discussed theoretically.¹¹⁵ The heterolytic cleavage of the Re—Re bond in the complexes $[(OC)_4RePR_2O]_2^-$ with alkanediylbis(trifluoromethanesulfonates) also results in the formation of intermediates, which are subjected to similar degradation mechanisms.⁵

2. Metallacycloalkanes as Reactive Intermediates

In a variety of organic syntheses, metallacycloalkanes with different ring sizes are important reactive intermediates. They are formed in different ways, as pointed out in Section II.A. Several degradation mechanisms are responsible for their decomposition, which results in the formation of organic products and the corresponding catalytically active species. Stabilization of metallacycloalkanes results on introduction of a donor atom adjacent to the metal.

¹⁰⁸ J. X. McDermott, J. F. White, and G. M. Whitesides, *J. Am. Chem. Soc.* **95**, 4451 (1973).

¹⁰⁹ P. J. Davidson, M. F. Lappert, and R. Pearce, *Chem. Rev.* **76**, 219 (1976).

¹¹⁰ P. W. Hall, R. J. Puddephatt, K. R. Seddon, and C. F. H. Tipper, *J. Organomet. Chem.* **81**, 423 (1974).

¹¹¹ R. DiCosimo and G. M. Whitesides, *J. Am. Chem. Soc.* **104**, 3601 (1982).

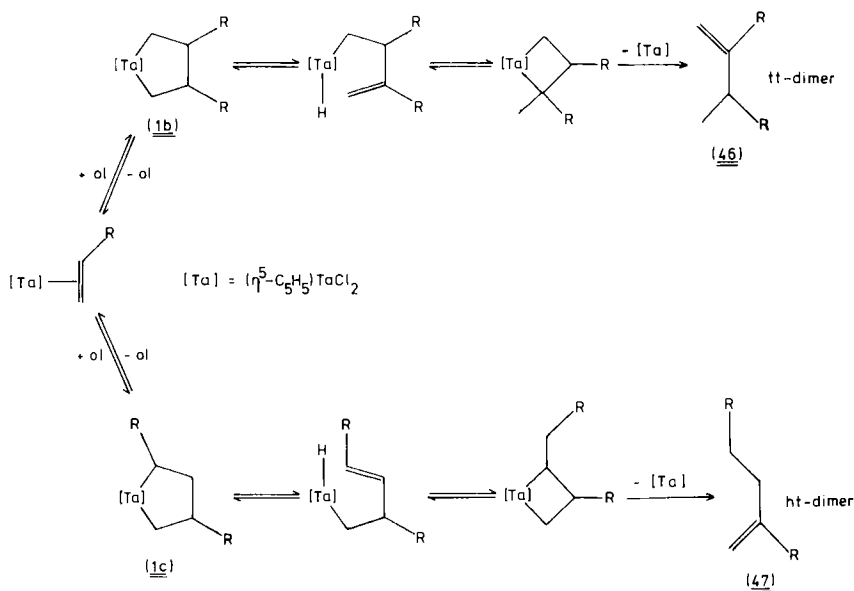
¹¹² J. X. McDermott, J. F. White, and G. M. Whitesides, *J. Am. Chem. Soc.* **98**, 6521 (1976).

¹¹³ J. D. Fellman, G. A. Rupprecht, and R. R. Schrock, *J. Am. Chem. Soc.* **101**, 5099 (1979).

¹¹⁴ S. J. McLain and R. R. Schrock, *J. Am. Chem. Soc.* **100**, 1315 (1978).

¹¹⁵ R. J. McKinney, D. L. Thorn, R. Hoffmann, and A. Stockis, *J. Am. Chem. Soc.* **103**, 2595 (1981).

a. *Alkene Dimerization.* Transition metals can catalyze the dimerization of olefins to linear dimers.¹⁴ For example, α,β - and β,β' -disubstituted tantalacyclopentanes (**1b**) are active intermediates in the catalytic dimerization of olefins to a mixture of tail-to-tail (tt) dimers **46** and head-to-tail (ht) dimers **47**, respectively, at rates of the order of one turnover/h at 30°C. Deuterium-labeling studies showed that each tantalacyclopentane ring contracts to a tantalacyclobutane ring, initiated by a β -hydrogen transfer, which then rearranges selectively to the tt or ht dimer (Scheme 14).¹⁹ The final step



SCHEME 14

is a reductive elimination. An alternative to the thermodynamically more favored ring contraction mechanism is the appearance of an allylic intermediate.

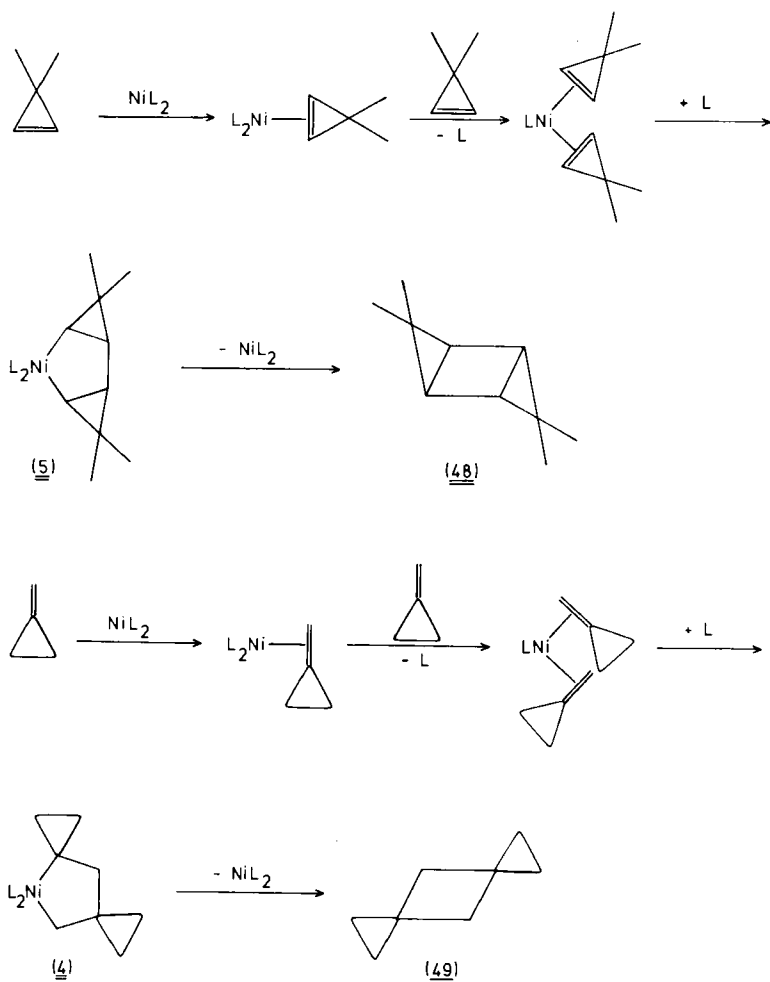
In the absence of CO, **8a** decomposes even at -30°C to give *cis*- and *trans*-butene in a ratio of 1:2 and Fe₃(CO)₁₂. β -Hydrogen transfer and reductive elimination are also involved.^{30,31}

b. *Cyclodimerization.* The intervention of a five-membered metallacyclic intermediate in metal-catalyzed [2 + 2] cycloaddition reactions was first demonstrated by Osborn *et al.*¹¹⁶ and by Binger *et al.*¹¹⁷ after it was

¹¹⁶ A. R. Fraser, P. H. Bird, S. A. Bezman, I. R. Shapley, R. White, and J. A. Osborn, *J. Am. Chem. Soc.* **95**, 597 (1973).

¹¹⁷ P. Binger, G. Schroth, and J. McMeeking, *Angew. Chem., Int. Ed. Engl.* **13**, 465 (1974).

postulated by Noyori *et al.*¹¹⁸ Cyclodimers from simple, unstrained, unsaturated hydrocarbons were reported to be formed via nickelacyclopentanes (**3b**).¹⁴ The cyclodimerization of strained olefins such as methylenecyclopropanes or dimethylcyclopropanes, giving **48** and **49**, was systematically investigated by Binger *et al.*^{23-26,119} In each case a nickelacyclopentane ring is the key compound (Scheme 15). Compounds **48** and **49** result from a reduc-



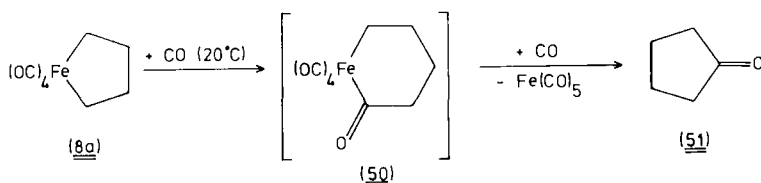
SCHEME 15

¹¹⁸ R. Noyori, T. Ishigami, N. Hayashi, and H. Takaya, *J. Am. Chem. Soc.* **95**, 1674 (1973).

¹¹⁹ M. J. Doyle, J. McMeeking, and P. Binger, *J. C. S. Chem. Commun.*, 376 (1976).

tive elimination. Rearrangement of **4** and **5** leads to six- and seven-membered nickelacycles.^{23-26,119} Instead of nickel, cobalt can be used for cyclodimerizations; the corresponding cobaltacyclopentanes are involved.²⁷

c. *Cyclopentanone Synthesis.* An important reaction is the "CO insertion" into a metal-carbon σ bond of metallacyclopentanes to form cyclopentanones. Pentacarbonyliron is useful for the olefin carbonylation, leading to derivatives of cyclopentanone.¹²⁰⁻¹²³ Weissberger *et al.*^{124,125} first proposed tetracarbonylferracyclopentanes as reactive intermediates. In a theoretical analysis Stockis and Hoffmann¹³ were concerned with the ring-closure reaction of $(\eta^2\text{-C}_2\text{H}_4)_2\text{Fe}(\text{CO})_3$ ¹²⁶ to **8a**.^{30,31} Koerner von Gustorf *et al.*¹²⁷ and Grevels *et al.*^{128,129} isolated stable substituted ferracyclopentanes photochemically. Titana-,⁵² molybda-,⁵⁸ nickela-,^{16,130} pallada-,¹³¹ and ferracyclopentanes^{30,31} also react with carbon monoxide to give cyclopentanone **51** (Scheme 16). The expected insertion product **50**, from which **51** is reduc-



SCHEME 16

tively eliminated, cannot be detected.^{30,31} In the presence of CO, **8a** is thermally much more stable and reacts only at 20°C.

d. *Alkene Metathesis.* Metallacyclobutanes are well-established intermediates in alkene metathesis, where the interconversion to alkene-carbene

¹²⁰ J. Mantzaris and E. Weissberger, *J. Am. Chem. Soc.* **96**, 1873 (1974); *Tetrahedron Lett.*, 2815 (1972).

¹²¹ A. Speert, J. Gelan, M. Anteunis, A. P. Marchand, and P. Laszlo, *Tetrahedron Lett.*, 2271 (1973).

¹²² J. Grandjean, P. Laszlo, and A. Stockis, *J. Am. Chem. Soc.* **96**, 1622 (1974).

¹²³ H. Schmid, P. Naab, and K. Hayakawa, *Helv. Chim. Acta* **61**, 1427 (1978).

¹²⁴ E. Weissberger and P. Laszlo, *Acc. Chem. Res.* **9**, 209 (1976).

¹²⁵ E. Weissberger and G. Page, *J. Am. Chem. Soc.* **99**, 147 (1977).

¹²⁶ J. C. Mitchener and M. S. Wrighton, *J. Am. Chem. Soc.* **105**, 1065 (1983).

¹²⁷ F. W. Grevels, D. Schulz, and E. A. Koerner von Gustorf, *Angew. Chem., Int. Ed. Engl.* **13**, 534 (1974).

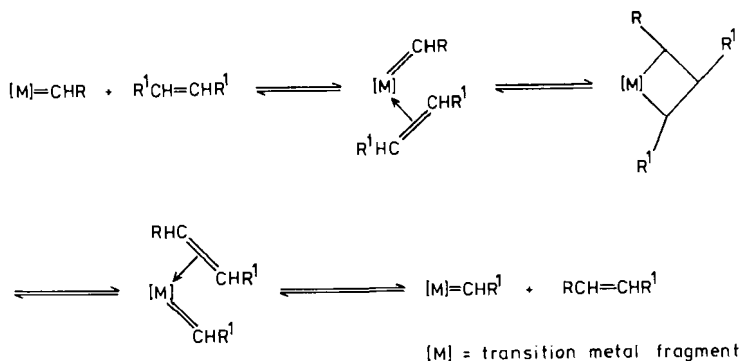
¹²⁸ F. W. Grevels, U. Feldhoff, J. Leitich, and C. Krüger, *J. Organomet. Chem.* **118**, 79 (1976).

¹²⁹ B. E. Foulger, F. W. Grevels, D. Hess, E. A. Koerner von Gustorf, and J. Leitich, *J. C. S. Dalton Trans.*, 1451 (1979).

¹³⁰ R. H. Grubbs and A. Miyashita, *J. Organomet. Chem.* **161**, 371 (1978).

¹³¹ P. Diversi, G. Ingrosso, A. Lucherini, and S. Murtas, *J. C. S. Dalton Trans.*, 1633 (1980).

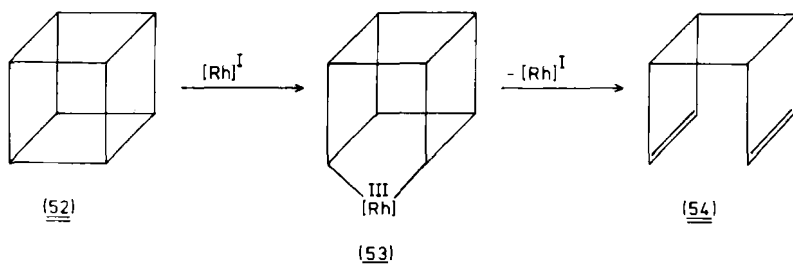
complex intermediates is involved in the propagation steps (Scheme 17).^{81,132} The best model is that based on titanocene derivatives, where the



SCHEME 17

interconversion of carbene-like species with metallacyclobutanes has been demonstrated directly.^{83-86,133} The kinetics and stereochemistry of the titanacyclobutane-titaniummethylene interconversion was investigated by Grubbs *et al.*^{84-86,134} Metallacyclobutanes can be regarded as precursors for the formation of carbene complexes.^{19,49-51,135}

e. *Valence Isomerization.* The occurrence of metallacycloalkane **53** as an intermediate is also assumed in the valence isomerization of cubane **52** to *syn*-tricyclooctadiene derivatives **54** (Scheme 18).¹³⁶



[Rh] = [Rh(dien)Cl]₂, dien = norbornadiene, cyclooctadiene

SCHEME 18

¹³² N. Calderon, J. P. Lawrence, and E. A. Ofstead, *Adv. Organomet. Chem.* **17**, 449 (1979).

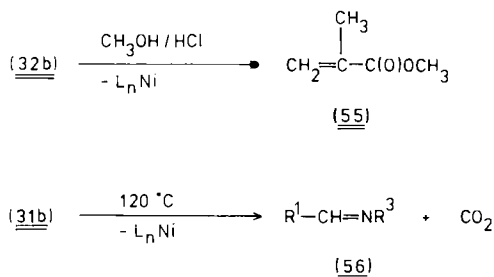
¹³³ F. N. Tebbe, G. W. Parshall, and G. S. Reddy, *J. Am. Chem. Soc.* **100**, 3611 (1978).

¹³⁴ K. C. Ott, J. B. Lee, and R. H. Grubbs, *J. Am. Chem. Soc.* **104**, 2942 (1982).

¹³⁵ A. Miyashita and R. H. Grubbs, *Tetrahedron Lett.* **22**, 1255 (1981).

¹³⁶ L. Cassar, P. E. Eaton, and J. Halpern, *J. Am. Chem. Soc.* **92**, 3515 (1970).

f. *C—C Bonding.* The oxidative addition of CO₂ together with alkenes,⁷¹ 1,3-dienes,⁷² and 1,2-dienes,⁷⁴ or isocyanates with imines⁷⁵ and aldehydes,⁷⁶ respectively, to nickel(0) complexes leads to a C—C bond formation. Saturated and unsaturated carbonic acid derivatives,^{71,72} methacrylic acid esters (**55**),⁷⁴ unsymmetrically substituted ureas,⁷⁵ and imines (**56**)⁷⁶ have been isolated (Scheme 19).



SCHEME 19

3. Ring Contractions and Ring Expansions

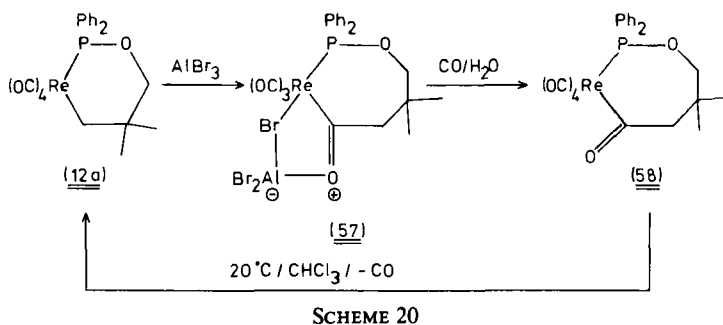
Thermally stable metallacycloalkanes with a metal adjacent to a donor atom such as phosphorus or arsenic have been extensively used to study insertion reactions into a metal–carbon σ bond, leading to ring-expansion products. A very facile reaction is SO₂ insertion, proceeding even at -40°C , in the case of the oxaphosphamangana- and -rhenacycloalkanes **10e**,⁹⁵ **10b**,^{32,137} and **12**.^{5,35,36,137} In contrast, “CO insertions” are successful with manganacycloalkanes³² only at elevated temperatures and CO pressures. Such reactions are reversible, decarbonylation leading to the original (contracted) ring.

When the metal-coordinated carbon monoxide in **12a** is activated with a Lewis base like AlBr₃, the colorless adduct **57** is isolated. This takes up carbon monoxide without elevated pressure at 20°C . On hydrolysis and cleavage of the aluminum residue it is transformed into the ring-expanded, colorless, thermally labile insertion product **58**.^{35,137} Carbon monoxide is reeliminated starting at 20°C in solution. Scheme 20 reveals the first “CO insertion” into a Re—C σ bond with an sp^3 -hybridized carbon atom.

Either SO₂ or, with the exception of rhenium and nickel, CO can be inserted in the same way into metal–carbon σ bonds of the four- to seven-membered metallacycles **38–44**.^{7,8,38,89–94,138} In each case the ring-expanded

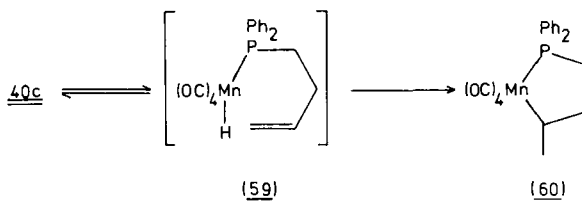
¹³⁷ E. Lindner, G. von Au, H.-J. Eberle, and S. Hoehne, *Chem. Ber.* **115**, 513 (1982).

¹³⁸ E. Lindner and G. Funk, *J. Organomet. Chem.* **216**, 393 (1981).



heterocycles were produced. The four-membered, ring-strained heterocycle **40a** reacts at 50°C at atmospheric CO pressure to give a thermodynamically favored five-membered cyclic acyl compound.¹³⁸ CO₂ can be inserted into the Mn—C bond of **40a**, leading to a six-membered metallacycle with an MnOC(O)CH₂ skeleton.¹³⁹ The mangana- and molybdacyclopropanes **14** and **15**^{37,38} do not react with either SO₂ or CO. Electronic factors are largely responsible for this behavior. The IR spectra of the ring-expanded products are characterized by their antisymmetric and symmetric SO₂¹⁴⁰ or C=O absorptions, both shifted to lower wavelengths. The structures of representative SO₂ and CO insertion products are proved by X-ray investigations.^{137,138} An SO₂ insertion into both Pd—C bonds of a palladacyclopentane was reported.⁵⁶

The six-membered manganacycle **40c** is susceptible to ring contraction.⁸ On warming **40c** in *n*-hexane in a sealed tube at 100°C, β-hydrogen transfer gives the unstable intermediate **59**. Subsequent intramolecular addition according to Markownikoff affords the contracted ring **60** (Scheme 21).

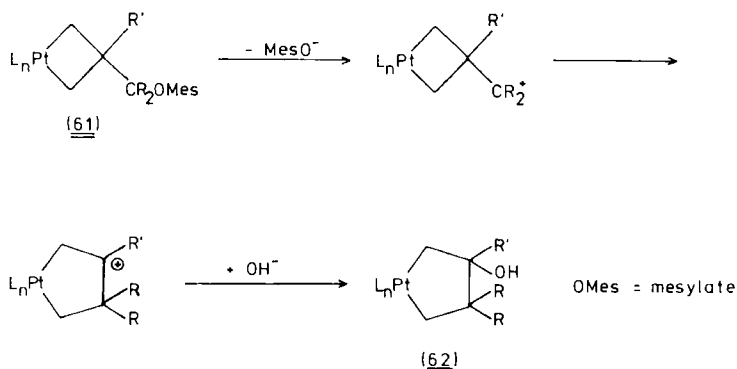


An interesting metallacyclobutane (**61**) to metallacyclopentane ring expansion was observed by Burton and Puddephatt.¹⁴¹ The mechanism is demonstrated in Scheme 22.

¹³⁹ A. Behr, U. Kanne, and G. Thelen, *J. Organomet. Chem.* **269**, C1 (1984).

¹⁴⁰ G. Vitzthum and E. Lindner, *Angew. Chem., Int. Ed. Engl.* **10**, 315 (1971).

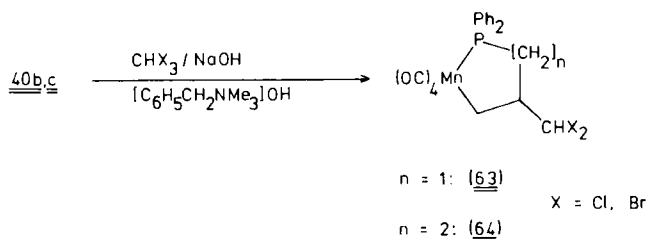
¹⁴¹ J. T. Burton and R. J. Puddephatt, *J. Am. Chem. Soc.* **104**, 4242 (1982).



SCHEME 22

4. Carbene Insertion Reactions

Dihalocarbenes, like CCl_2 or CBr_2 , generated *in situ* by phase transfer catalysis are inserted into a β C—H bond of the five- and six-membered heterocycles **40b,c** to give the functionalized metallacycles **63** and **64**¹⁴² (Scheme 23). A precondition for this reaction is a *trans*-M—C—C—H



SCHEME 23

arrangement for optimal M—C—C σ/π overlap. The reactivity of the $Mn—C$ σ bond is decreased to such a degree that no reaction takes place with SO_2 or CO . The CX_2 functions in **63** and **64** cannot be hydrolyzed or reduced. With CH_3MgI no methylation is possible.

¹⁴² E. Lindner, F. Zinsser, H. A. Mayer, W. Hiller, and R. Fawzi, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **40B**, 615 (1985).

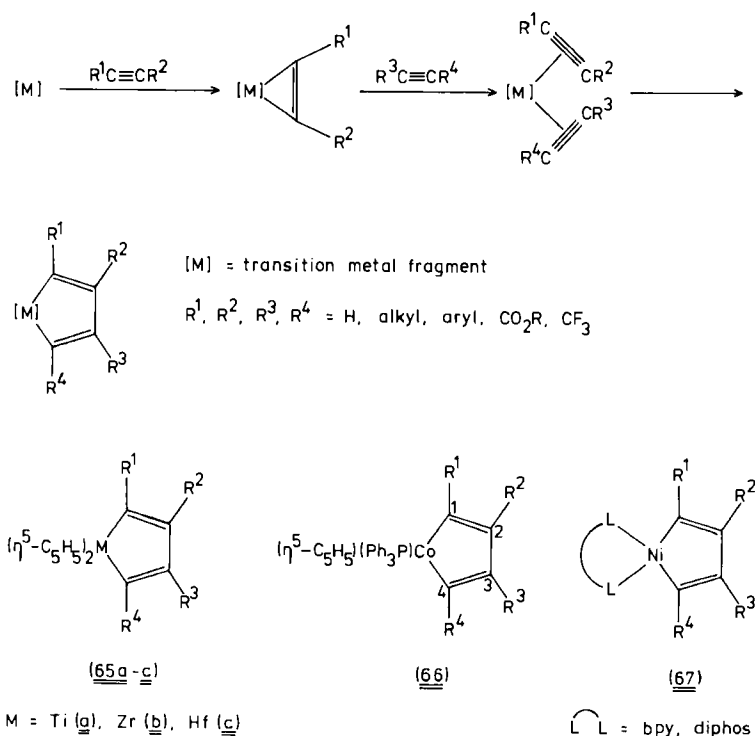
III. Metallacycloalkenes without and with Additional Heteroatoms

Among the metallacycloalkenes with different ring size, metallacycloprenes and -pentadienes are to be mentioned because they are involved as intermediates in the cyclotrimerization of alkynes to benzene derivatives,¹⁴³ and in this section attention is mainly directed to such species. Cotrimerizations also are possible with alkyne-like systems.

A. METHODS FOR SYNTHESSES

1. Cyclization of Bisalkyne Complexes

Substantial evidence has been adduced for the stepwise formation of metallacycloprenes and -pentadienes, starting from appropriate metal complexes and acetylenes. Scheme 24 demonstrates a general route to the cycli-



SCHEME 24

¹⁴³ G. Ville, K. P. C. Vollhardt, and M. J. Winter, *J. Am. Chem. Soc.* **103**, 5267 (1981).

zation of bisalkyne complexes. Heterocycles **65–67** are obtained either thermally or photochemically.

Metallacyclopentadienes of titanium (**65a**),^{144–146} zirconium (**65b**),^{145,147} hafnium (**65c**),¹⁴⁵ cobalt (**66**)^{148,149} nickel (**67**),¹⁵⁰ and palladium¹⁵¹ have been reported. The reasons for the apparent absence of bond-length equalization in metallacyclopentadienes, a precondition for the delocalization of electrons, was discussed by Thorn and Hoffmann.¹⁵²

The formation of **66** by reaction of acetylenes with ($\eta^5\text{-C}_5\text{H}_5$)(Ph_3P)Co(acetylene) has been investigated in detail.¹⁵³ Kinetic studies indicate the intermediacy of ($\eta^5\text{-C}_5\text{H}_5$)Co(acetylene)₂ (Scheme 24), which cyclizes to a coordinatively unsaturated cobaltacyclopentadiene by a spontaneous oxidative coupling. Regioselectivity of the cyclization process is controlled by steric rather than by electronic character of substituents.

2. Cyclization of Alkyne/Alkene Complexes

The cobaltacycloprenes **68** react with 1,2-disubstituted olefins to form metallacyclopentenenes **70** (Scheme 25).¹⁵⁴ A kinetic study indicates an intermediate (**69**) in which acetylene and olefin are simultaneously coordinated to cobalt. Depending on the substituents $\text{R}^1\text{--R}^4$, regio- and stereoisomers could be isolated.

With the exception of ($\eta^5\text{-C}_5\text{Me}_5$)Ta(HC \equiv CH)Cl₂ (**71**), the corresponding alkyne complexes of tantalum do not react with olefins; **71** cyclizes with ethylene at 80°C to give the tantalacyclopentene **72** (Scheme 25).¹⁵⁵

¹⁴⁴ G. Fachinetti, C. Floriani, F. Marchetti, and M. Mellini, *J. C. S. Dalton Trans.*, 1398 (1978), and references cited herein.

¹⁴⁵ D. J. Sikora and M. D. Rausch, *J. Organomet. Chem.* **276**, 21 (1984), and references cited herein.

¹⁴⁶ V. B. Shur, E. G. Berkovich, M. E. Vol'pin, B. Lorenz, and M. Wahren, *J. Organomet. Chem.* **228**, C36 (1982).

¹⁴⁷ V. Skibbe and G. Erker, *J. Organomet. Chem.* **241**, 15 (1983).

¹⁴⁸ H. Yamazaki and Y. Wakatsuki, *J. Organomet. Chem.* **139**, 157 (1977).

¹⁴⁹ L. P. McDonnell Bushnell, E. R. Evitt, and R. G. Bergman, *J. Organomet. Chem.* **157**, 445 (1978).

¹⁵⁰ J. J. Eisch, A. A. Aradi, and K. I. Han, *Tetrahedron Lett.* **24**, 2073 (1983).

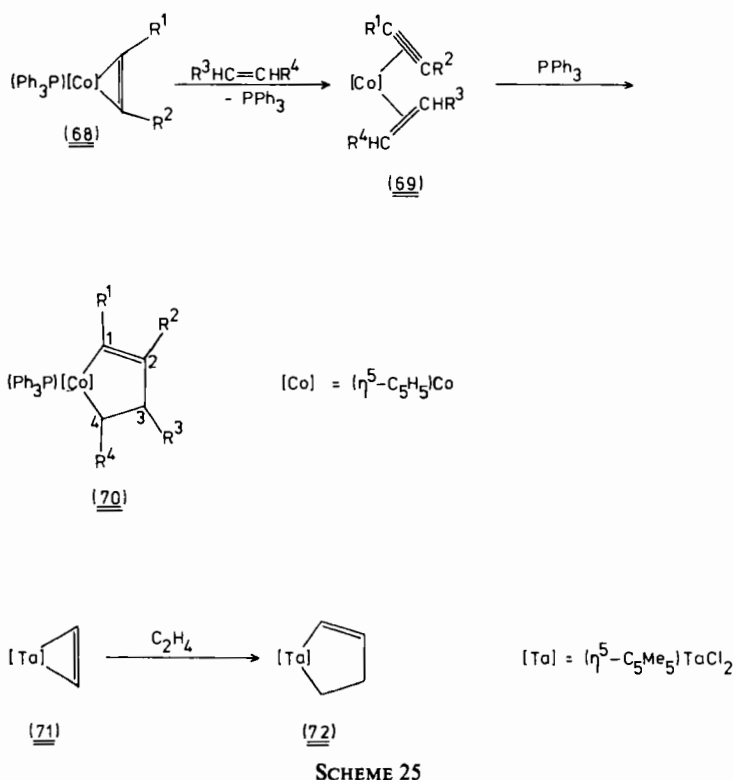
¹⁵¹ L. D. Brown, K. Itoh, H. Suzuki, K. Hirai, and J. A. Ibers, *J. Am. Chem. Soc.* **100**, 8232 (1978).

¹⁵² D. L. Thorn and R. Hoffmann, *Nouv. J. Chim.* **3**, 39 (1979).

¹⁵³ Y. Wakatsuki, O. Nomura, K. Kitaura, K. Morokuma, and H. Yamazaki, *J. Am. Chem. Soc.* **105**, 1907 (1983).

¹⁵⁴ Y. Wakatsuki, K. Aoki, and H. Yamazaki, *J. Am. Chem. Soc.* **101**, 1123 (1979).

¹⁵⁵ G. Smith, R. R. Schrock, M. R. Churchill, and W. J. Youngs, *Inorg. Chem.* **20**, 387 (1981).



3. Cyclization of Alkylthio Complexes with Alkynes

Carbon disulfide has proved to be a versatile ligand, it forms complexes with almost every transition metal. In most monometallic CS_2 compounds, CS_2 is η^2 -coordinated to give a thiametallacyclopropane (Scheme 26).¹⁵⁶⁻¹⁶⁰ A molecular orbital analysis of the bonding capabilities of carbon disulfide toward transition metal fragments, using the extended Hückel method, was carried out by Hoffmann *et al.*¹⁶¹ The thiaferracyclopropane 73 is a starting

¹⁵⁶ J. A. Ibers, *Chem. Soc. Rev.* **11**, 57 (1982).

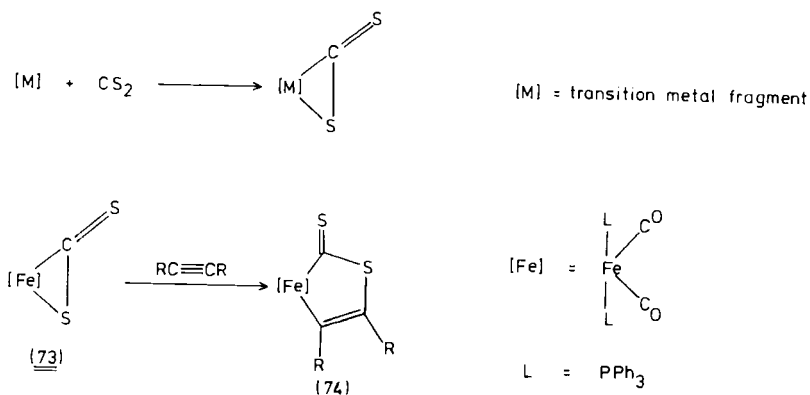
¹⁵⁷ T. R. Gaffney and J. A. Ibers, *Inorg. Chem.* **21**, 2854, 2857, 2860 (1982).

¹⁵⁸ M. G. Mason, P. N. Swebston, and J. A. Ibers, *Inorg. Chem.* **22**, 411 (1983).

¹⁵⁹ C. C. Frazier, R. F. Kline, and D. D. Barck, *Inorg. Chem.* **20**, 4009 (1981).

¹⁶⁰ H. Le Bozec, P. H. Dixneuf, A. J. Carty, and N. J. Taylor, *Inorg. Chem.* **17**, 2568 (1978).

¹⁶¹ C. Mealli, R. Hoffmann, and A. Stockis, *Inorg. Chem.* **23**, 56 (1984).



SCHEME 26

material for the synthesis of several interesting compounds.¹⁶²⁻¹⁶⁵ With alkynes the thiaferracyclopentenones **74** are formed (Scheme 26).^{166,167} This type of reaction was discovered by Wakatsuki *et al.*¹⁶⁸ with rhodium.

When activated alkynes are allowed to react with the thiolates **75a,b**, the thiametallacyclobutenes **76a,b** are isolated.^{169,170} In some cases a carbonyl ligand is involved, leading to five-membered thiametallacyclopentenones, e.g., **78** (Scheme 27).^{171,172} The CO group in **78** can also be adjacent to SR¹.

4. Photolysis of Metal Complexes in the Presence of Alkynes

Five-membered oxametallacyclopentadienes **82a,b** are obtained photochemically from **79a,b** and alkynes. The intermediates **80a,b** and **81a,b** were isolated and characterized (Scheme 28).¹⁷³

¹⁶² T. G. Southern, U. Oehmichen, J. Y. Le Marouille, H. Le Bozec, D. Grandjean, and P. H. Dixneuf, *Inorg. Chem.* **19**, 2976 (1980).

¹⁶³ A. J. Carty, P. H. Dixneuf, A. Gorgues, F. Hartstock, H. Le Bozec, and N. J. Taylor, *Inorg. Chem.* **20**, 3929 (1981).

¹⁶⁴ M. Ngounda, H. Le Bozec, and P. H. Dixneuf, *J. Org. Chem.* **47**, 4000 (1982).

¹⁶⁵ H. Le Bozec and P. H. Dixneuf, *J. C. S. Chem. Commun.*, 1462 (1983).

¹⁶⁶ H. Le Bozec, A. Gorgues, and P. H. Dixneuf, *J. C. S. Chem. Commun.*, 573 (1978).

¹⁶⁷ H. Le Bozec, A. Gorgues, and P. H. Dixneuf, *Inorg. Chem.* **20**, 2486 (1981).

¹⁶⁸ Y. Wakatsuki, H. Yamazaki, and H. Iwasaki, *J. Am. Chem. Soc.* **95**, 5781 (1973).

¹⁶⁹ M. J. Barrow, J. L. Davidson, W. Harrison, D. W. A. Sharp, G. A. Sim, and F. B. Wilson, *J. C. S. Chem. Commun.*, 583 (1973).

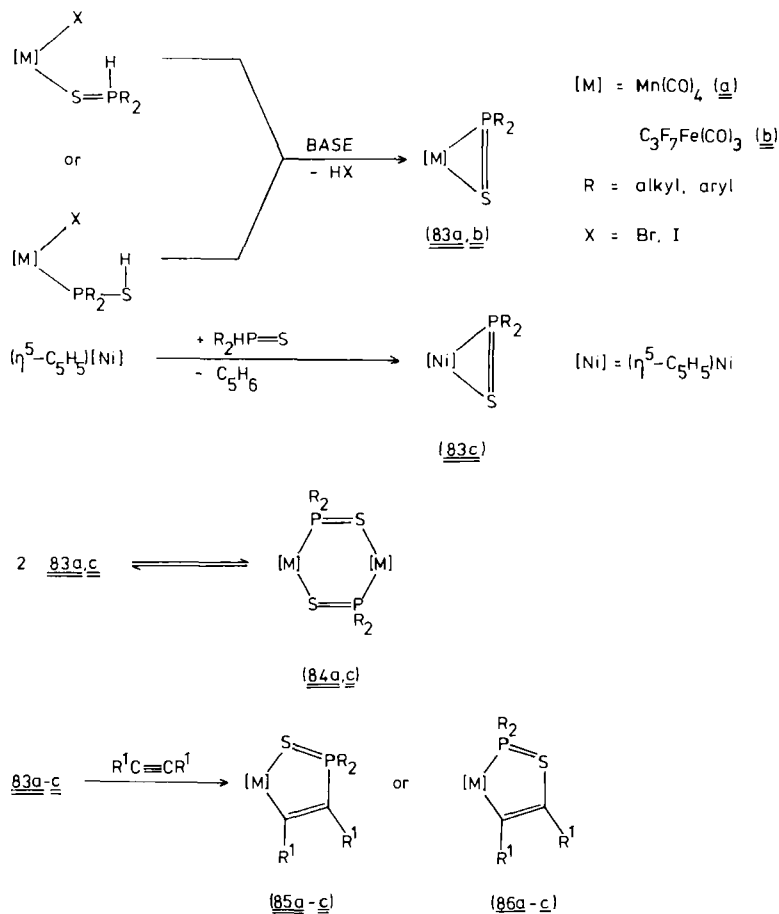
¹⁷⁰ J. L. Davidson and D. W. A. Sharp, *J. C. S. Dalton Trans.*, 2283 (1975).

¹⁷¹ J. L. Davidson, M. Shiralian, L. Manojlovic-Muir, and K. W. Muir, *J. C. S. Chem. Commun.*, 30 (1979).

¹⁷² J. L. Davidson, *J. C. S. Chem. Commun.*, 597 (1979).

¹⁷³ H. G. Alt, *Angew. Chem., Int. Ed. Engl.* **23**, 766 (1984), and references cited herein.

comparable atomic radii and electronegativities of phosphorus and sulfur. The three-membered thiaphosphametallacyclopropenes of manganese (**83a**),^{174,175} iron (**83b**),^{176,177} and nickel (**83c**)^{178,179} are accessible by elimination reactions^{174-177,180,181} or in the case of **83c** by the action of $R_2HP=S$ on nickelocene (Scheme 29). Compounds **83a,c** are very unstable and dimerize



SCHEME 29

¹⁷⁴ E. Lindner, A. Rau, and S. Hoehne, *Angew. Chem., Int. Ed. Engl.* **20**, 787 (1981).

¹⁷⁵ E. Lindner, A. Rau, and S. Hoehne, *Chem. Ber.* **114**, 3281 (1981).

¹⁷⁶ E. Lindner, C.-P. Krieg, W. Hiller, and R. Fawzi, *Angew. Chem., Int. Ed. Engl.* **23**, 523 (1984).

¹⁷⁷ E. Lindner, C.-P. Krieg, W. Hiller, and R. Fawzi, *Chem. Ber.* **118**, 1398 (1985).

¹⁷⁸ E. Lindner, F. Bouachir, and W. Hiller, *J. Organomet. Chem.* **210**, C37 (1981).

¹⁷⁹ E. Lindner, F. Bouachir, and S. Hoehne, *Chem. Ber.* **116**, 46 (1983).

¹⁸⁰ E. Lindner and H. Dreher, *J. Organomet. Chem.* **105**, 85 (1976).

¹⁸¹ E. Lindner and B. Schilling, *Chem. Ber.* **110**, 3889 (1977).

immediately to **84a,c**. Between **83a,c** and **84a,c** in solution there exists a dissociative equilibrium.^{174,178,179} The $-I$ effect of the C_3F_7 group in **83b** in a trans position to the sulfur atom stabilizes the three-membered ring to such an extent that it can be isolated and identified. Oligomerization or dimerization is not observed in solution, even at $50^\circ C$.^{176,177} Compounds **83a-c** are trapped with electrophilic alkynes to give thiaphosphametallacyclopentadienes.¹⁷⁴⁻¹⁷⁹ Insertion into a metal-phosphorus bond is preferred over insertion into a metal-sulfur bond, e.g., **85a-c** and **86a-c** (Scheme 29). In contrast to **86a-c**, the S isomeric species **85a-c** are thermally stable. The instability of **83a-c** is due to a weak metal-phosphorus and metal-sulfur bond. When the metal is replaced by a $4d$ or $5d$ transition element like molybdenum or tungsten,¹⁸²⁻¹⁸⁴ the corresponding $P=S$ -containing metalacycles do not react with alkynes.

6. Oxidative Addition of Unsaturated Substrates to Transition Metals

Nickel(0) complexes undergo oxidative addition reactions with alkynes to give nickelacyclopentadienes¹⁵⁰ and also react under certain conditions with carbon dioxide or isocyanates to form oxanickelacyclopentenones (**87**)¹⁸⁵⁻¹⁸⁸ or azanickelacyclopentenones (**88**)¹⁸⁹ (Scheme 30). In both cases the chelating basic ligand TMEDA (tetramethylethylenediamine) influences the reaction strongly.

Nickel(0) complexes activate alkynes and carbon monoxide.¹⁹⁰⁻¹⁹² The latter is used either coordinated to nickel [e.g., $(bpy)Ni(CO)_2$] or as gas. Nickelacyclopentenediones (**89**) are detected as reactive intermediates (Scheme 30).

¹⁸² D. H. M. W. Thewissen, *J. Organomet. Chem.* **192**, 115 (1980).

¹⁸³ H. P. M. M. Ambrosius, J. H. Noordik, and G. J. A. Ariaans, *J. C. S. Chem. Commun.*, 832 (1980).

¹⁸⁴ M. Luksza, K. Jörg, and W. Malisch, *Inorg. Chim. Acta* **85**, L49 (1984).

¹⁸⁵ G. Burkhart and H. Hoberg, *Angew. Chem., Int. Ed. Engl.* **21**, 76 (1982).

¹⁸⁶ H. Hoberg, D. Schaefer, and G. Burkhart, *J. Organomet. Chem.* **228**, C21 (1982).

¹⁸⁷ H. Hoberg and D. Schaefer, *J. Organomet. Chem.* **238**, 383 (1982).

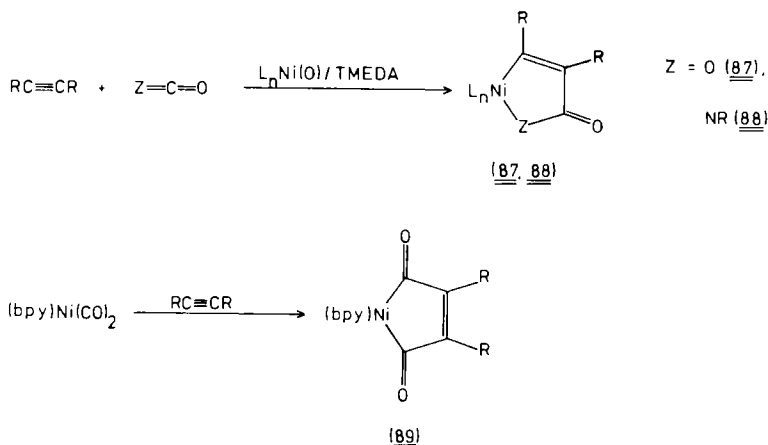
¹⁸⁸ H. Hoberg, D. Schaefer, G. Burkhart, C. Krüger, and M. J. Romão, *J. Organomet. Chem.* **266**, 203 (1984).

¹⁸⁹ H. Hoberg and B. W. Oster, *J. Organomet. Chem.* **234**, C35 (1982); **252**, 359 (1983).

¹⁹⁰ H. Hoberg and A. Herrera, *Angew. Chem., Int. Ed. Engl.* **19**, 927 (1980); **20**, 876 (1981).

¹⁹¹ A. Herrera and H. Hoberg, *Synthesis*, 831 (1981).

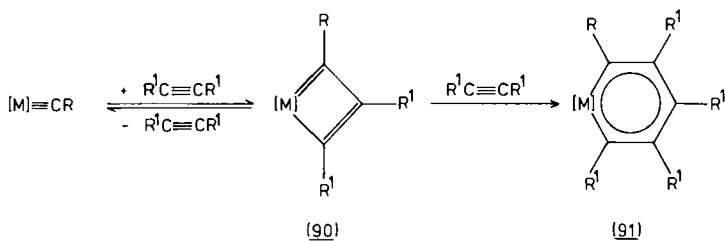
¹⁹² A. Herrera, H. Hoberg, and R. Mynott, *J. Organomet. Chem.* **222**, 331 (1981).



SCHEME 30

7. Addition of Alkynes to Metal Carbyne Complexes

A general approach to metallacyclobutadienes (**90**) is the reaction of carbyne complexes with alkynes. These four-membered rings are intermediates in the metathesis of acetylenes.^{193–195} Compounds **90** ($M = W$) offer a possibility for ring expansion to give a planar tungstenabenzene intermediate (**91**) (Scheme 31). The structure of a derivatized osmabenzene has been reported.¹⁹⁶



SCHEME 31

¹⁹³ M. R. Churchill, J. W. Ziller, J. H. Freudenberger, and R. R. Schrock, *Organometallics* **3**, 1554 (1984).

¹⁹⁴ J. H. Freudenberger, R. R. Schrock, M. R. Churchill, A. L. Rheingold, and J. W. Ziller, *Organometallics* **3**, 1563 (1984).

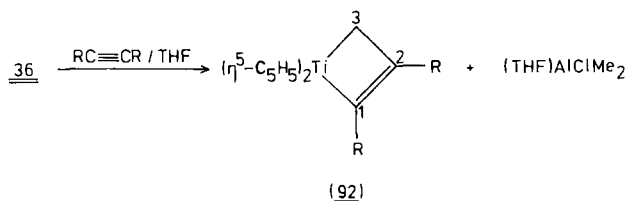
¹⁹⁵ R. R. Schrock, S. F. Pedersen, M. R. Churchill, and J. W. Ziller, *Organometallics* **3**, 1574 (1984).

¹⁹⁶ G. P. Elliot, W. R. Roper, and J. M. Waters, *J. C. S. Chem. Commun.*, 811 (1982).

The stability of early-transition-metal metallacyclobutadienes was calculated by Bursten.¹⁹⁷

8. Reaction of Alkynes with Titanium-Aluminum-Alkyl Complexes

Compound **36** reacts with alkynes in THF to produce titanacyclobutenes (**92**) (Scheme 32).^{198,199} It is useful to draw comparisons between titanacy-



SCHEME 32

clobutenes (**92**) and titanacyclobutanes (**37**), which may be transient intermediates in olefin metathesis reactions catalyzed by **36**. Conditions that were found to favor synthesis of **92** also significantly enhance rates of olefin metathesis catalyzed by **36**.

B. STRUCTURE AND PHYSICAL PROPERTIES

Metallacycloprenes, -butenes, -pentenes, -butadienes, and -pentadienes usually are only available when they are stabilized by suitable substituents. Like their saturated analogs they are air sensitive and their solubility depends on the polarity of the substituents. A heteroatom adjacent to the metal increases the stability of metallacycloalkenes.

1. X-Ray Crystallography

X-Ray crystallographic investigations have been carried out on representatives of all the important metallacycloalkenes. The first key product of alkyne trimerization is a metallacycloprenene, obtained by oxidative addi-

¹⁹⁷ B. E. Bursten, *J. Am. Chem. Soc.* **105**, 121 (1983).

¹⁹⁸ F. N. Tebbe and R. L. Harlow, *J. Am. Chem. Soc.* **102**, 6149 (1980).

¹⁹⁹ R. J. McKinney, T. H. Tulip, D. L. Thorn, T. S. Coolbaugh, and F. N. Tebbe, *J. Am. Chem. Soc.* **103**, 5584 (1981).

tion of an acetylene to a transition metal complex. Of interest is a comparison between the carbon-carbon bond length in metallacycloprenes and the $P=S$ bond distance in thiophosphametallacycloprenes, such as **83b**, which is the starting material for the cyclocotrimerization of thiophosphinites with alkynes. In typical titana-,¹⁴⁴ vanada-,²⁰⁰ nickela-,¹⁴⁴ niobia-,¹⁰³ tantal-,¹⁵⁵ tungstena-,¹⁴⁴ and platinacycloprenes,²⁰¹ the C—C bond lengths vary from 125 to 135 pm (average value 128 pm), which is between a triple and a double bond. The $P=S$ distance in **83b**^{176,177} is 201.1 pm, a value, which is between a double and a single bond. Similar short $P=S$ bond lengths were also found in the dimeric species **84a,c**.^{178,202}

The next step in the alkyne cyclo- and cyclocotrimerization is the formation of metallacyclopentadienes of the type **65–67**^{144–151} and thiophosphametallacyclopentadienes (**85**),^{174–179} respectively. For a wide range of metals and ligands structure determinations of metallacyclopentadienes show, with some exceptions, bond lengths consistent with localized double bonds.¹⁵² In several titana-, hafna-, cobalta-, rhoda-, and palladacyclopentadienes,¹⁵² the bond-length sequence (short/long/short) varies between 133 and 138 pm on the one side and from 139 to 151 pm on the other. Structure determinations for the heterometallacyclopentadienes **85a–c** have shown $P=S$ distances of 199.6, 200.1, and 200.4 pm, and C—C bond lengths of 135.6 and 135.0 pm.^{174–179} All of the five-membered rings deviate but little from planarity.

The geometry of the cobaltacyclopentene **70** ($R^1 = Rh$; $R^2 = R^3 = R^4 = CO_2CH_3$) is quite different from that of the cobaltacyclopentadiene **66** ($R^1 = R^2 = R^3 = R^4 = C_6F_5$). In **70**, C-4 is displaced by 58.3 pm from the plane formed by Co, C-1, C-2, and C-3, away from the $\eta^5-C_5H_5$ ring. The Co— sp^2 -carbon distance of 194.7 pm is somewhat shorter than those in **66** (199.5 and 199.3 pm), whereas the Co— sp^3 -carbon distance of 209.7 pm in **70** is longer than the corresponding values in **23a** (202.5 and 202.4 pm).⁵³ The short C—C bond in **70** is 137.5 pm and the other two C—C bonds have distances of 152.7 and 151.3 pm.

An X-ray crystal structure shows **92** to be a planar titanacyclobutene ($R = C_6H_5$). The C-1—C-2 (134.4 pm) and C-2—C-3 (153.7 pm) distances are within the ranges expected for C—C double and single bonds, respectively.^{198,199}

The WC_3 ring systems in **90** are planar within the limits of experimental error. The average $W-C_\alpha$ distances are 187 pm, the $W-C_\beta$ distances vary between 188 and 195 pm depending on the ligands attached to tungsten. The

²⁰⁰ J. L. Petersen and L. Griffith, *Inorg. Chem.* **19**, 1852 (1980), and references cited herein.

²⁰¹ D. H. Farrar and N. C. Payne, *Inorg. Chem.* **20**, 821 (1981).

²⁰² E. Lindner, C.-P. Krieg, S. Hoehne, and A. Rau, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **36B**, 1487 (1981).

C—C bond distances within the WC_3 systems in **90** are nearly equivalent (142.9 and 143.7 pm) or differ only slightly (143.3 and 146.7 pm).¹⁹⁴

2. Spectroscopic Properties

Some information about structural and bonding properties can be gained from the 1H - and ^{13}C -NMR spectra. An insight into the composition and the degradation mechanisms of metallacycloalkenes is possible by an analysis of their mass spectra. The interpretation of IR spectra is useful if the rings are provided with functional groups or the metals have ligands that give rise to intensive and characteristic IR absorptions.

a. Infrared Spectra. For the different metallacyclopropenes $[M]-CR=CR$ ¹⁴⁴ a $\nu(C=C)$ stretching vibration was found in the range 1740–1880 cm^{-1} , which is shifted to longer wavelengths compared with the free acetylene ligand.

The P=S vibration of the three- and five-membered metallacycles **83b** and **85a–c**, respectively, absorbs between 570 and 522 cm^{-1} , according to the double-bond character of the P=S function.^{174–179} In accordance with the thiaphosphametallacyclopentadiene structure in **85a–c**, the C—C stretching vibration in the ring is assigned between 1550 and 1482 cm^{-1} .^{174–179}

Compound **85a** and the P isomer **86a** are easily distinguished by the different position of the $C\equiv O$ bands because phosphorus is a better π acceptor than sulfur.¹⁷⁵ The three CO ligands in **83b** and **85b** are always arranged equatorially, the middle CO molecule being located in the trans position to the sulfur (**85b** in *n*-hexane: 2110 w, 2053 vs, 2042 cm^{-1} s; R = C_2H_5 ; R¹ = $CO_2C_6H_{11}$) or phosphorus atom (**83b** in *n*-hexane: 2100 w, 2042 sh, 2036 cm^{-1} vs; R = C_2H_5).^{176,177}

b. 1H -NMR Spectra. If an appropriate substituent is attached to the phosphorus atom of **85** and **86**, the isomers are easily distinguished. In the 1H -NMR spectra of **85a,c** (R = CH_3), the $P(CH_3)_2$ protons appear as a doublet because of ^{31}P coupling. Because of the direct metal–phosphorus bond in **86a,c**, this doublet occurs with a smaller coupling constant.^{174,175,179} Otherwise 1H -NMR spectroscopy is useful only for the identification of the substituents of the metallacycloalkenes.

c. ^{13}C -NMR Spectra. Few ^{13}C -NMR shifts are available in the literature for metallacycloalkenes. Compound **71** in C_6D_6 (relative to TMS) shows a doublet centered at δ 218.1 with a coupling constant of $^1J_{CH} = 189$ Hz. The

$^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum of **72** exhibits four resonances in addition to the two at δ 124.0 and 12.3 due to the $\eta^5\text{-C}_5\text{Me}_5$ ligand. In the ^1H gated decoupled ^{13}C spectrum, the resonances at δ 210.7 and 150.8 appear as doublets ($^1J_{\text{CH}} = 140$ Hz) while those at δ 96.9 and 44.1 appear as triplets ($^1J_{\text{CH}} = 123$ Hz). Therefore they are assigned to the olefin and aliphatic carbon atoms C_α and C_β , respectively.¹⁵⁵ Compound **85a** ($\text{R} = \text{CH}_3$, $\text{R}^1 = \text{CO}_2\text{CH}_3$) in the $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum exhibits five signals [δ 20.36 (s, $^1J_{\text{PC}} = 52.5$ Hz); 51.33, 52.46 (s); 128.29 (s); 159.20 (d, $^1J_{\text{PC}} = 27.4$ Hz)], which can be assigned to the carbon atoms of the $\text{P}(\text{CH}_3)_2$, OCH_3 , MnC , and PC groups, respectively.

d. *Mass Spectra.* Metals of metallacycloalkenes provided with carbonyl,^{174–177} perfluoroalkyl,^{176,177} cyclopentadienyl,^{178,179} or other less polar ligands are volatile enough to be suitable for electron-impact mass spectra. In general, the CO molecules eliminate first, followed by fragmentation of the ring skeleton. The more polar metallacycloalkenes can only be detected by the field-desorption method; usually only the molecular peak appears.

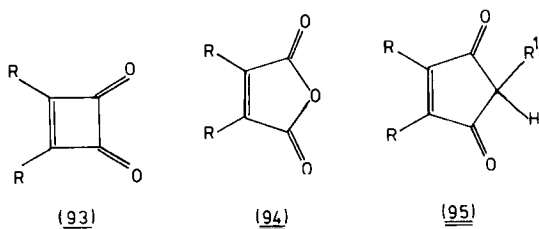
C. REACTIONS OF METALLACYCLOALKENES

Like their metallacycloalkane analogs, the chemical behavior of the unsaturated species is quite different from the corresponding heterocycles without a metal atom. Metallacycloalkenes appear also as reactive intermediates, e.g., in alkyne trimerization or cotrimerization with heterosystems or in alkyne metathesis. Some important examples are given in the following sections.

1. *Synthesis of Cycloalkenediones, Cyclopentenones, Cyclohexa- and Cyclopentadienones, Alkenes, and Dienes*

Nickelacyclopentenediones (**89**) react with maleic anhydride (MA) or carbon monoxide to give cyclobutenediones (**93**), oxygen to cyclopentenediones (**94**), and geminal dihalides to **95** (Scheme 33). The mechanism of these reactions has been explained.^{190–192}

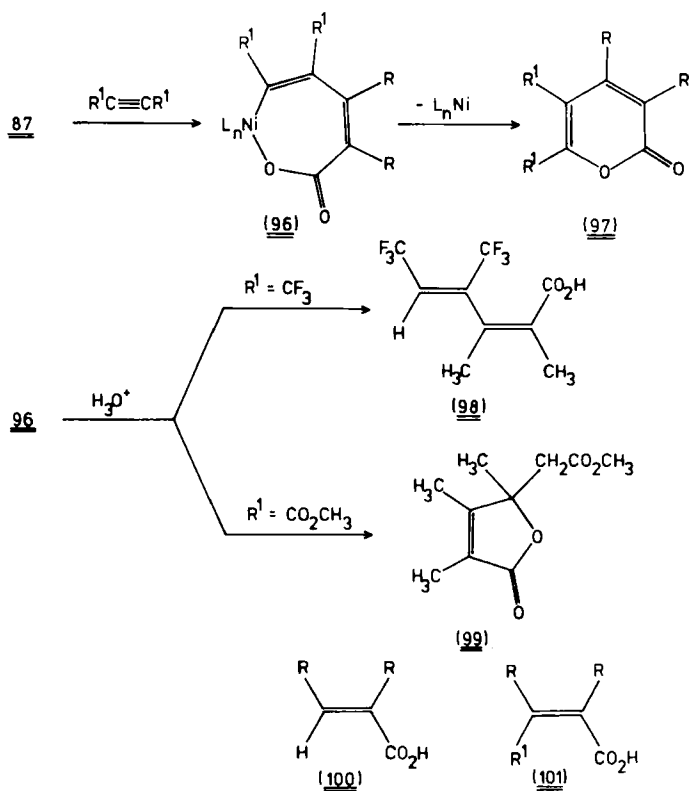
Oxanickelacyclopentenones (**87**) react in many different ways. With carbon monoxide, derivatives of **94** are formed.^{185–188} Insertion of an alkyne leads to the ring-expanded seven-membered oxanickelacycloheptadienones **96**, which on hydrolysis yield oxacyclopentenones (**99**) or dienes (**98**). Reductive elimination of the organic substrate from **96** is also observed to give



SCHEME 33

oxacyclohexadienones (**97**). Alkenes **100** and **101**, respectively, are formed by hydrolysis of **87** and by reaction with alkyl halides (Scheme 34).¹⁸⁵⁻¹⁸⁸

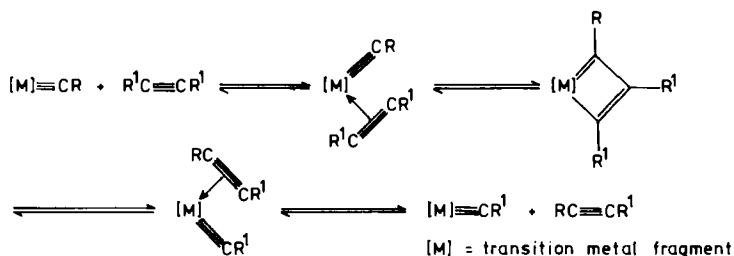
In a similar manner, azanickelacyclopentenones (**88**) react according to Scheme 34 to give corresponding aza compounds, in which oxygen is replaced by nitrogen.¹⁸⁹



SCHEME 34

2. Alkyne Metathesis

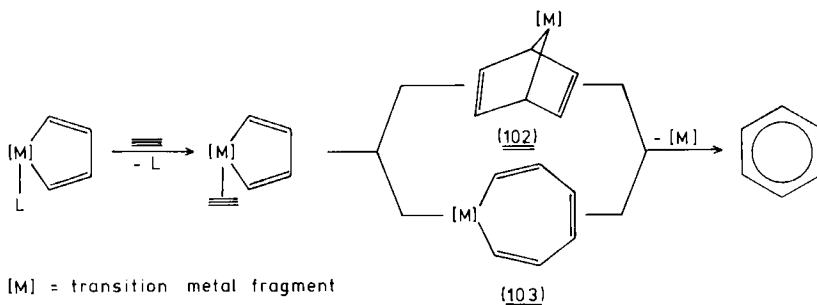
Metallacyclobutadienes are known to be intermediates in alkyne metathesis (Scheme 35).¹⁹³⁻¹⁹⁵ Preferred metathesis catalysts are tungsten complexes, which metathesize acetylenes either rapidly by a dissociative mechanism, i.e., via formation of putative $W(CEt)(OR)_3$, or slowly by an associative mechanism in relatively noncoordinating solvents.¹⁹³⁻¹⁹⁵ The metathesis of tungsten-tungsten triple bonds with acetylenes and nitriles to give alkylidyne and nitrido complexes is also reported.²⁰³



SCHEME 35

3. Cyclotrimerization of Alkynes

The cyclotrimerization of alkynes by transition metal complexes proceeds via metallacycloprenes and -cyclopentadienes; depending on the alkyne, the products are metallacycloheptatrienes (**103**) or -bicycloheptadienes (**102**) (Scheme 36).^{10,153,204,205} The first mode is a Diels-Alder addition of a



SCHEME 36

²⁰³ R. R. Schrock, M. L. Listemann, and L. G. Sturgeoff, *J. Am. Chem. Soc.* **104**, 4291 (1982).

²⁰⁴ P. Caddy, M. Green, E. O'Brien, L. E. Smart, and P. Woodward, *J. C. S. Dalton Trans.*, 962 (1980).

²⁰⁵ D. R. McAlister, J. E. Bercaw, and R. G. Bergman, *J. Am. Chem. Soc.* **99**, 1666 (1977).

coordinated alkyne to the diene moiety of the metallole, generating bicyclic intermediate **102**. The second type is an insertion of a coordinated acetylene into a metal-carbon σ bond, leading to **103**. In either case the final step is reductive elimination of an arene with release of the coordinatively unsaturated metal fragment. Kinetic studies of these reactions have been carried out.^{154,205} Yamazaki *et al.* have provided evidence for the cobalt system **66**¹⁴⁸ during alkyne trimerization and isolated benzene derivatives with various substituents. Similar results are obtained with appropriate nickel complexes.¹⁵⁰ Electron-deficient alkynes also cyclotrimerize on heating in the presence of the rhodium complexes $[\text{Rh}(\text{CO})_2(\text{PPh}_3)_2]_2$.²⁰⁶ Bergman *et al.*²⁰⁷ and Wakatsuki *et al.*²⁰⁸ independently showed that more complicated alkynes, like bifunctional acetylenes and cobaltaindene or cobaltfluorene complexes, respectively, can be involved in cyclotrimerization reactions. Later, cyclotrimerization of substituted acetylenes to arenes with $\text{C}_8\text{H}_8\text{Ti}$ complexes or with TiCl_3 were reported. A cyclotrimerization mechanism is proposed, which involves the concerted trimerization of three acetylenes coordinated to a divalent titanium center.²⁰⁹

4. Cyclocotrimerization of Alkynes with Olefins, Nitriles, and Carbon Dioxide

In the course of the cyclotrimerization of alkynes with olefins, the cobaltacyclopentene **70** appears. When it reacts with alkynes, PPh_3 is replaced by $\text{RC}\equiv\text{CR}$, which is inserted into a $\text{Co}-\text{C}$ bond with formation of the trimerization product **104** (Scheme 37).¹⁵⁴

Effects of donor molecules on the palladium-catalyzed cyclotrimerization of acetylenes with olefins were investigated by Ibers *et al.*¹⁵¹

Cyclocotrimerization (mixed cyclotrimerization) of alkynes and nitriles by cobalt complexes leads to pyridine derivatives.^{11,210} The starting point is the cobaltacyclopentadiene **66**, which reacts with nitriles to give highly substituted pyridines. When $\text{R}^4 = \text{CO}_2\text{Me}$, nitriles react regioselectively such that the nitrogen atom in the resulting pyridine ring occupies a position away from the carbon to which the CO_2Me substituent is attached. Cobaltacycloprenes do not react with nitriles to form nitrogen-containing metallacy-

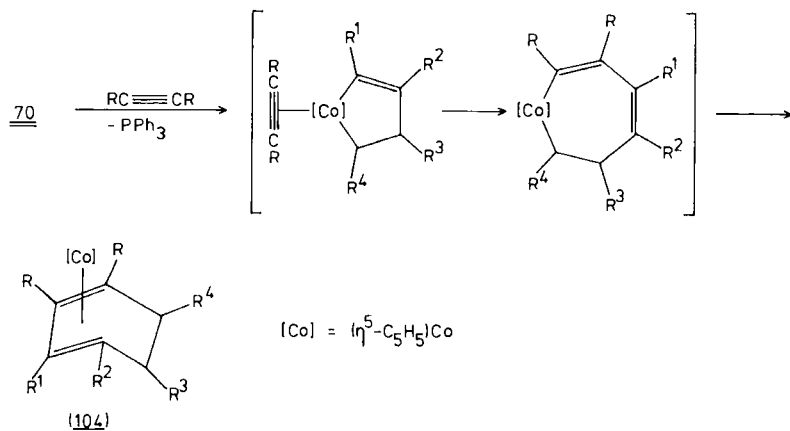
²⁰⁶ B. L. Booth, R. N. Haszeldine, and I. Perkins, *J. C. S. Dalton Trans.*, 2593 (1981).

²⁰⁷ L. P. McDonnell Bushnell, E. R. Evitt, and R. G. Bergman, *J. Organomet. Chem.* **157**, 445 (1978).

²⁰⁸ Y. Wakatsuki, O. Nomura, H. Tone, and H. Yamazaki, *J. C. S. Perkin II*, 1344 (1980).

²⁰⁹ M. E. E. Meijer-Veldman and H. J. de Liefde Meijer, *J. Organomet. Chem.* **260**, 199 (1984).

²¹⁰ Y. Wakatsuki and H. Yamazaki, *J. C. S. Dalton Trans.*, 1278 (1978).



SCHEME 37

cles. The mechanism of the stoichiometric and catalytic reaction is discussed.²¹⁰ An interesting feature is that η^6 -borinato groups as ligands at cobalt have unique effects on the chemo- and regioselectivity of the catalytic cocyclization of alkynes and nitriles. The turnover number of the conversion of acrylonitrile and acetylene to give 2-vinylpyridine is considerably enhanced. Cyano compounds with polar substituents such as amino or thio groups can also react. Homogeneous reaction of HCN with acetylene giving pyridine has now been achieved.²¹¹

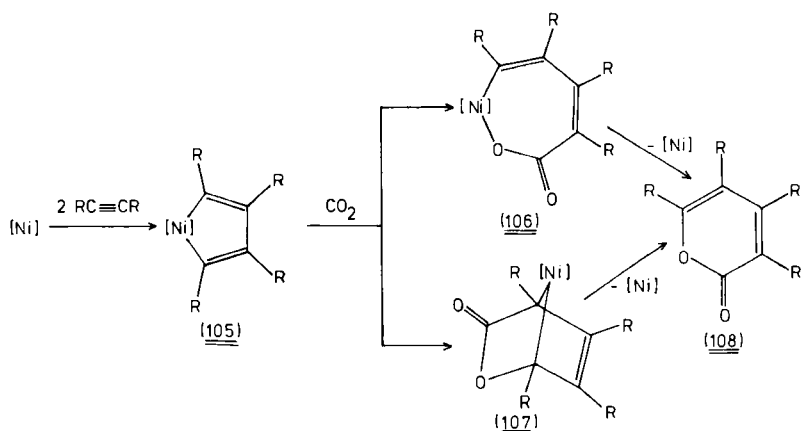
In contrast to nitriles, the reaction of **66** with isocyanides does not give trimerization products; rather an η^4 -iminocyclopentadienylcobalt complex is formed.²¹²

Ditertiary phosphane complexes of nickel were found to be effective in the formation of pyrone **108** by cyclocotrimerization of alkynes with carbon dioxide. The formation of the nickelacyclopentadiene **105** from two moles of alkyne and a nickel complex is followed by CO_2 insertion into a nickel-carbon bond to give the oxanickelacycloheptadienone **106**, which then eliminates **108** with intramolecular C—O coupling. Another route involving [4 + 2] cycloadditions of **105** with CO_2 in a Diels-Alder reaction to give **107** cannot be ruled out but is less probable because CO_2 does not undergo [4 + 2] cycloaddition with dienes. Addition of another alkyne to **105** results in the formation of a benzene derivative (Scheme 38).²¹³

²¹¹ H. Bönemann, W. Brijoux, R. Brinkmann, and W. Meurers, *Helv. Chim. Acta* **67**, 1616 (1984).

²¹² H. Yamazaki and Y. Wakatsuki, *Bull. Chem. Soc. Jpn.* **52**, 1239 (1979).

²¹³ Y. Inoue, Y. Itoh, H. Kazama, and H. Hashimoto, *Bull. Chem. Soc. Jpn.* **53**, 3329 (1980).



SCHEME 38

5. Hetero $\text{P}=\text{S}$ Analogous Cyclotrimerization with Alkynes

The $\text{P}=\text{S}$ -containing metallacyclopentadienes **85a,b** can be regarded as intermediates in the cyclocyclotrimerization of thiophosphinites with alkynes. They are kinetically labile toward alkynes and react via elimination of CO and insertion into the $\text{M}-\text{C}$ σ bond to produce metallacycloheptatrienes (**110a,b**) with vacant coordination sites, which immediately rearrange via reductive $\text{C}-\text{S}$ coupling to the bicyclo[2.2.1]heptadienes **111a,b** (Scheme 39). With the $\text{P}=\text{S}$ analogs, the course of the cyclotrimerization with alkynes shows, among other things, that the triply bonded C atoms of the newly incorporated alkyne occupy positions C-1 and C-6 in **111a,b**. When the alkyne $\text{HC}\equiv\text{CR}^2$ is used, regiospecific insertion results with exclusive formation of the isomer with H at C-6.^{174-177,214,215} Compound **85a** reacts with isocyanides under substitution of CO by RNC. Insertion into a $\text{Mn}-\text{C}$ σ bond is not observed.²⁰² Action of alkynes to the isocyanide substitution products affords again **111a**. This observation may be considered as a confirmation of the occurrence of **109a**.

When **111a** is treated with CO ²¹⁴ or Ce(IV) salts,²¹⁶ cleavage of the PR_2 group takes place with almost quantitative formation of the thiophene derivative **112** (Scheme 39).²¹⁵ Under catalytic hydrogenation conditions with Raney nickel, ring contraction via selective sulfur extrusion to the bicyclo[2.1.1]hexene **113** occurs.^{215,216}

²¹⁴ E. Lindner, A. Rau, and S. Hoehne, *Angew. Chem., Int. Ed. Engl.* **18**, 534 (1979).

²¹⁵ E. Lindner, A. Rau, and S. Hoehne, *J. Organomet. Chem.* **218**, 41 (1981).

²¹⁶ E. Lindner, A. Rau, and S. Hoehne, *Angew. Chem., Int. Ed. Engl.* **20**, 788 (1981).

This Page Intentionally Left Blank

Tricyclic Compounds with a Central Pyrimidine Ring and One Bridgehead Nitrogen

ISTVÁN HERMECZ AND LELLE VASVÁRI-DEBRECZY

*CHINOIN, Pharmaceutical and Chemical Works Ltd., Research Centre,
1325 Budapest, Hungary*

I. Introduction	282
II. Tricyclic Compounds Containing a Three-Membered Ring	284
A. Azirino[1,2- <i>c</i>]quinazolines (Ring System Type I)	284
B. Angular Annelated Ring Systems with Nitrogen in the Ring Angle (Type II)	285
1. Syntheses	285
2. Reactions	287
3. Physicochemical Properties	289
C. Azirino[2,1- <i>b</i>]quinazolines (Ring System Type III)	289
III. Other Angular Annelated Ring Systems with Nitrogen Away from the Ring Angle (Type I)	290
A. Syntheses.	290
1. From Quinazolines	290
2. Miscellaneous Syntheses	294
B. Reactions	295
C. Physicochemical Properties	296
D. Applications.	297
IV. Other Angular Annelated Ring Systems with Nitrogen in the Ring Angle (Type II)	297
A. Syntheses.	297
1. From Anthranilic Acid Derivatives and from Quinazolines	297
2. Miscellaneous Syntheses	309
B. Reactions.	312
1. Hydrolysis and Ring Cleavage	312
2. Reduction, Oxidation	313
3. Active Methylene Group Reactions	314
4. Miscellaneous Reactions	314
C. Physicochemical Properties	316
D. Applications.	317
V. Other Linearly Annelated Ring Systems (Type III)	317
A. Naturally Occurring Derivatives	317
B. Syntheses.	322
1. From Anthranilic Acid and Its Derivatives.	322
2. From α -Amino Nitrogen Heterocycles	331
3. From Δ^1 -Azacyloalkenes with 2-Aminobenzaldehyde	334

4. From 2-Aminobenzylamines and Their Derivatives	335
5. By Ring Transformations	339
6. Miscellaneous Syntheses	340
C. Reactions.	344
1. Hydrolysis and Ring Opening	344
2. Hydrogenation and Reduction	346
3. Dehydrogenation and Oxidation	351
4. Quaternization, N-Alkylation, N-Dealkylation, N-Acylation, and N-Deacylation	354
5. Electrophilic Substitution	355
6. Active Methylene Group Reactions and Some Subsequent Changes . . .	356
7. Ring Transformation	362
8. Miscellaneous Reactions	365
D. Physicochemical Properties	370
E. Applications.	375
VI. Appendix	380
A. Angular Annelated Ring Systems with Nitrogen Away from the Ring Angle (Type I)	380
B. Angular Annelated Ring Systems with Nitrogen in the Ring Angle (Type II)	381
C. Linearly Annelated Ring Systems (Type III)	382
Note Added in Proof	385

I. Introduction

Tricyclic compounds with a central pyrimidine ring and one bridgehead nitrogen can be divided into three types.

Type I: Angular annelated ring systems in which rings A and C are attached to positions 3,4 and 5,6 of the central pyrimidine ring, i.e., with nitrogen away from ring angle.

Type II: Angular annelated ring systems in which rings A and C are attached to positions 1,2 and 5,6 of the central pyrimidine ring, i.e., with nitrogen in ring angle.

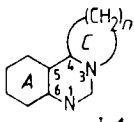
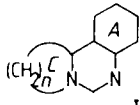
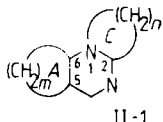
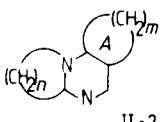
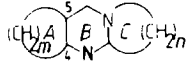
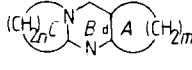
Type III: Linearly annelated ring systems in which rings A and C are attached to positions 1,2 and 4,5 of the central pyrimidine ring.

Known ring systems of types I–III, together with their structural diagrams and chemical names as used in *Chemical Abstracts*, are listed in Table I.

In the present review the primary chemical literature up to the end of 1984 has been surveyed. *Chemical Abstracts* Subject and Chemical Substance Indexes up to and including Volume 100 have been searched. A few further references from later literature are added in an Appendix.

The only previous review of the chemistry of pyrrolo[1,2-*a*]quinazolines, pyrrolo[1,2-*a*]quinazolines, pyrrolo[2,1-*b*]quinazolines, and pyrido[2,1-*b*]-

TABLE I
TRICYCLIC RING SYSTEMS WITH A CENTRAL PYRIMIDINE RING AND
ONE BRIDGEHEAD NITROGEN ATOM

Type I			
		I-1	I-2
Size of ring C ($n + 2$)	Structural diagram	Chemical name as used in <i>Chemical Abstracts</i>	
3	I-1	Azirino[1,2- <i>c</i>]quinazoline	
5	I-1	Pyrrolo[1,2- <i>c</i>]quinazoline	
6	I-2	Pyrido[1,2- <i>c</i>]quinazoline	
7	I-2	Azepino[1,2- <i>c</i>]quinazoline	
Type II			
		II-1	II-2
Size of ring A ($m + 2$)	Size of ring C ($n + 2$)	Structural diagram	Chemical name
3	5	II-2	Cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>]pyrimidine
6	3	II-1	Azirino[1,2- <i>a</i>]quinazoline
5	6	II-2	Cyclopenta[<i>e</i>]pyrido[1,2- <i>a</i>]pyrimidine
6	5	II-1	Pyrrolo[1,2- <i>a</i>]quinazoline
6	6	II-1	Pyrido[1,2- <i>a</i>]quinazoline
6	7	II-2	Azepino[1,2- <i>a</i>]quinazoline
Type III			
		III-1	III-2
Size of ring A ($m + 2$)	Size of ring C ($n + 2$)	Structural diagram	Chemical Name
6	3	III-1	Azirino[2,1- <i>b</i>]quinazoline
5	5	III-2	Cyclopenta[<i>d</i>]pyrrolo[1,2- <i>a</i>]pyrimidine
5	6	III-2	Cyclopenta[<i>d</i>]pyrido[1,2- <i>a</i>]pyrimidine
6	5	III-1	Pyrrolo[2,1- <i>b</i>]quinazoline
6	6	III-2	Pyrido[2,1- <i>b</i>]quinazoline
5	7	III-2	Cyclopenta[4,5]pyrimido[1,2- <i>a</i>]azepine
7	5	III-1	Cyclohepta[<i>d</i>]pyrrolo[1,2- <i>a</i>]pyrimidine
6	7	III-2	Azepino[2,1- <i>b</i>]quinazoline

(Continued)

TABLE I (Continued)

7	6	III-1	Cyclohepta[<i>d</i>]pyrido[1,2- <i>a</i>]pyrimidine
7	7	III-2	Cyclohepta[4,5]pyrimido[1,2- <i>a</i>]azepine
5	8	III-2	Cyclopenta[4,5]pyrimido[1,2- <i>a</i>]azocine
8	5	III-1	Cycloocta[<i>d</i>]pyrrolo[1,2- <i>a</i>]pyrimidine
6	8	III-2	Azocino[2,1- <i>b</i>]quinazoline
8	6	III-1	Cycloocta[<i>d</i>]pyrido[1,2- <i>a</i>]pyrimidine
7	8	III-2	Cyclohepta[4,5]pyrimido[1,2- <i>a</i>]azocine
8	7	III-1	Cycloocta[4,5]pyrimido[1,2- <i>a</i>]azepine
8	8	III-2	Cycloocta[4,5]pyrimido[1,2- <i>a</i>]azocine
6	9	III-2	Azonino[2,1- <i>b</i>]quinazoline
6	11	III-2	Azocycloundecino[2,1- <i>b</i>]quinazoline

quinazolines is that by Mosby,¹ who found 35 references to these ring systems while covering the literature up to 1957. These publications have also been included in the present work.

A number of linearly annelated tricyclic compounds are known as alkaloids. Certain types of tricyclic nitrogen bridgehead compounds have aroused interest because of their valuable pharmacological properties. They are also used as photographic sensitizers and fiber-reactive dyes.

From each type of ring system, those compounds containing a three-membered ring are surveyed separately in the next section, as a consequence of their special syntheses and reactivities. Subsequently, the ring systems of Types I, II, and III are discussed. The individual sections each deal first with syntheses and reactions, then with physicochemical properties, and briefly with utilization.

II. Tricyclic Compounds Containing a Three-Membered Ring

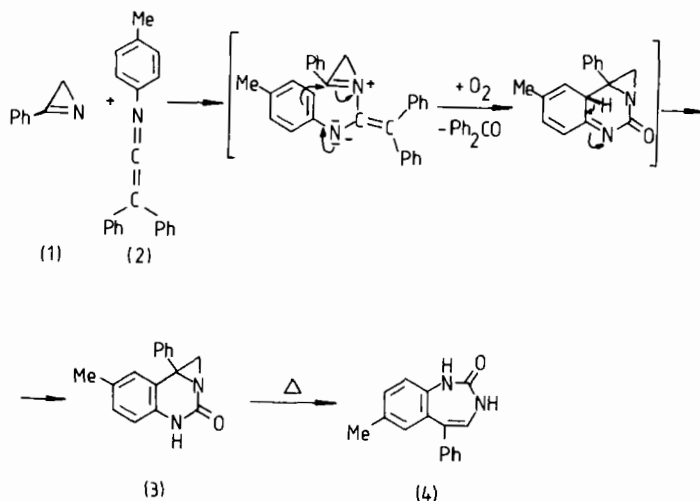
A. AZIRINO[1,2-*c*]QUINAZOLINES (RING SYSTEM TYPE I)

The only example of the ring system of Type I was prepared by Woerner *et al.*,² when 3-phenyl-2*H*-azirine (**1**) was treated with diphenylketene-*p*-tolylimine (**2**) in benzene at 65°C for 65 h; besides benzophenone, a 1 : 1 isomeric mixture of the azirino[1,2-*c*]quinazoline **3** and the 1,3-benzodiazepine **4** was formed. During heating in trichlorobenzene under a nitrogen atmosphere,

¹ W. L. Mosby, in "Heterocyclic Systems with Bridgehead Nitrogen Atoms" (A. Weissberger, ed.), Part I, p. 724; Part II, p. 1152. Wiley (Interscience), New York, 1961.

² F. P. Woerner, H. Reimlinger, and R. Merényi, *Chem. Ber.* **104**, 2789 (1971).

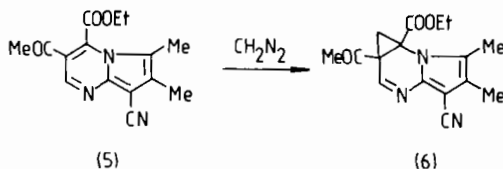
the azirinoquinazoline **3** was transformed irreversible into the 1,3-benzodiazepine **4**. Structure **3** was proved by its IR and ¹H-NMR spectra.



B. ANGULAR ANNELATED RING SYSTEMS WITH NITROGEN IN THE RING ANGLE (TYPE II)

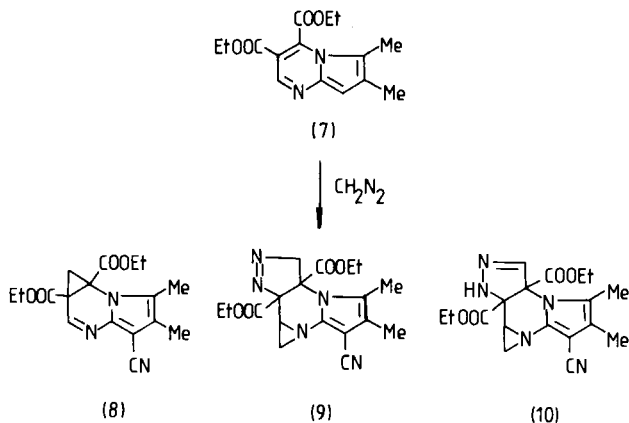
1. Syntheses

Treatment of the pyrrolo[1,2-*a*]pyrimidine **5** with an excess of diazomethane in diethyl ether at room temperature gave the cyclopropa[*e*]pyrrolo[1,2-*a*]pyrimidine **6** in 74% yield.³



The diester **7** under similar reaction conditions gave the cyclopropa[*e*]pyrrolo[1,2-*a*]pyrimidine **8** and the aziridino[*c*]pyrazolo[3,4-*a*]pyrrolo[1,2-*a*]pyrimidines **9** and **10** in yields of 40, 10, and 19%, respectively.³

³ T. Kurihara, K. Nasu, and Y. Adachi, *J. Heterocycl. Chem.* **20**, 81 (1983).



Sternbach and coworkers^{4,5} pointed out that the reactions of the 6-chloro-2-chloromethyl-1,2-dihydro-4-phenylquinazoline 3-oxides **11** with a base gives either the 1,3-dihydro-2*H*-azirino[1,2-*a*]quinazoline 4-oxides **13** or the 3*H*-1,4-benzodiazepine 4-oxide **15**. In the first step of the reaction the anion **12** is formed by abstraction of a proton from the 1-nitrogen. The intermediate anion **12** can rearrange to the ring-chain tautomer **14**. The relative stabilities of the two anions **12** and **14** are assumed to determine whether product **13** or **15** is formed. Thus when R is hydrogen or chloromethyl, the anion **12** is relatively sufficiently stable to allow the formation of the azirinoquinazoline **13**. If, however, R is the electron-releasing methyl group, the anion **12** is destabilized and is converted to anion **14**, which leads to benzodiazepine **15**. The solvent polarity also influences the stability of the anions **12** and **14**. In a nonpolar solvent (ether), the 5*H*-benzodiazepine **16** (R = Me) was obtained, which can be derived from anion **12** (R = Me) via the azirinoquinazoline **13** (R = Me). In a polar solvent (aqueous ethanol), however, the 3*H*-benzodiazepine **15** derived from anion **14** (R = Me) was the major product. As bases, potassium *tert*-butoxide and sodium hydride were used.⁴⁻⁷

A similar reaction was carried out by Yamada and co-workers.⁸⁻¹⁰ The

⁴ G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Lett.*, 2609 (1966).

⁵ G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Am. Chem. Soc.* **89**, 332 (1967).

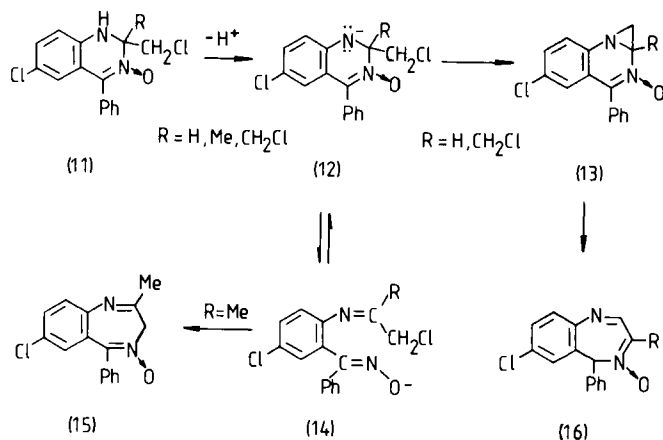
⁶ F. Hoffmann-La Roche and Co. A.-G., Netherlands Patent Appl. 6,515,759 [CA **65**, 15406 (1966)].

⁷ F. Hoffmann-La Roche and Co. A.-G., Netherlands Patent Appl. 6,614,923 [CA **67**, 90855 (1967)].

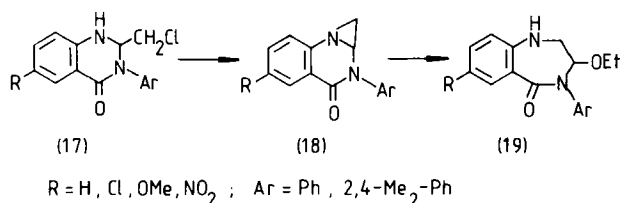
⁸ Y. Yamada, T. Oine, and I. Inoue, *Chem. Pharm. Bull.* **22**, 601 (1974).

⁹ T. Oine, Y. Yamada, I. Inoue, Japan Kokai 74/31,687 [CA **81**, 63695 (1974)].

¹⁰ T. Oine, Y. Yamada, I. Inoue, Japan Kokai 74/31,697 [CA **81**, 91564 (1974)].

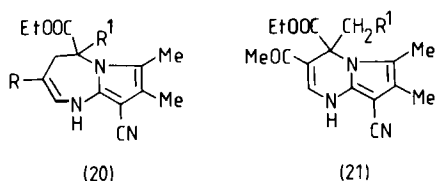


ring expansion reaction of the 2-chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (17) in ethanolic solution in the presence of a base afforded the benzodiazepines 19 via the azirinoquinazolines 18. If the 2-chloromethylquinazolinone 17 (R = H, Ar = Ph) was treated with potassium *tert*-butoxide in *tert*-butanol at room temperature, the azirinoquinazoline 18 (R = H, Ar = Ph) was isolated in 42% yield.

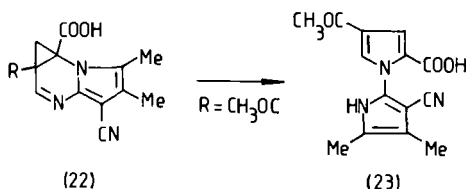


2. Reactions

Hydrogenolysis of the cyclopropane ring of the cyclopropa[*e*]pyrrolo-[1,2-*a*]pyrimidine 6, on catalytic hydrogenation in the presence of 5% palladium on carbon under atmospheric pressure, proceeded in two ways, giving rise to a mixture of the pyrrolodiazepine 20 (R = Ac, R¹ = H) and the pyrrolopyrimidine 21 (R¹ = H).³

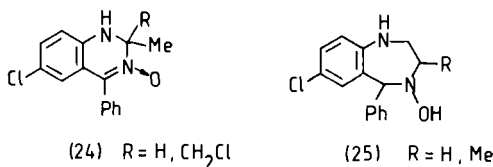


Under similar conditions, only the pyrrolodiazepine **20** ($R = \text{CO}_2\text{Et}$, $R^1 = \text{H}$) was isolated from the cyclopropa[*e*]pyrrolo[1,2-*a*]pyrimidine **8**. When **6** was refluxed in ethanol for 10 days, a mixture of **20** ($R = \text{Ac}$, $R^1 = \text{OEt}$) and **21** ($R^1 = \text{OEt}$) was obtained. Whereas treatment with potassium hydroxide in aqueous ethanol at room temperature transformed the acetylcyclopropapyrrolopyrimidine **6** into the 1-(2-pyrrolyl)pyrrole **23**, the diester **8** gave the monoester **22** ($R = \text{CO}_2\text{Et}$).³ The pyrrolylpyrrole **23** was likewise obtained from the sodium salt of **22** ($R = \text{Ac}$) by the action of hydrochloric acid. Ring transformation of the monoester **22** ($R = \text{CO}_2\text{Et}$) was not observed.³



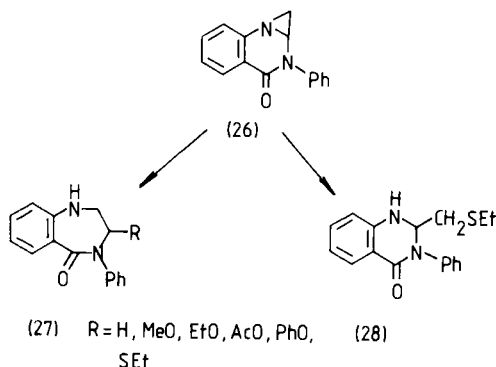
The azirinoquinazolines **13** are thermally unstable and isomerize readily to the 5*H*-benzodiazepines **16** through a [1,5] hydrogen shift. The methyl derivative of azirinoquinazoline **13** ($R = \text{Me}$) was converted to **16** ($R = \text{Me}$) when kept at room temperature.⁴ The azirinoquinazoline **13** ($R = \text{H}$) was transformed into **16** ($R = \text{H}$) under reflux conditions in toluene. Similarly, the chloromethyl derivative of the azirinoquinazoline **13** ($R = \text{CH}_2\text{Cl}$) was transformed into **16** ($R = \text{CH}_2\text{Cl}$) in dimethyl sulfoxide^{5,6} at 100°C.

Reduction of the azirinoquinazolines **13** resulted in cleavage of the aziridine ring in two different ways.⁴⁻⁶ Hydrogenation over Raney nickel gave the dihydroquinazoline *N*-oxides **24** ($R = \text{H}$, CH_2Cl).^{4,5} Reduction with sodium borohydride in diglyme, on the other hand, gave the tetrahydrobenzodiazepines **25** ($R = \text{H}$, Me).⁴⁻⁶ Reduction of the chloromethyl derivative **13** ($R = \text{CH}_2\text{Cl}$) was accompanied by loss of the side-chain chlorine and resulted in the 3-methylbenzodiazepine **25** ($R = \text{Me}$).^{5,6}



Yamada and co-workers^{8,9} studied the ring-opening reactions of the azirinoquinazoline **26** by the action of nucleophiles. Weak nucleophiles [ROH , PhSH , AcOH , and hydride anion ($\text{NaBH}_4/\text{diglyme}$)] bring about $\text{S}_{\text{N}}1$ type ring opening and afford the tetrahydrobenzodiazepinones **27**. Strong nu-

cleophiles (EtSH) tend to approach the aziridine ring from the less hindered side in an S_N2 manner to give the tetrahydroquinazolinone **28**. Reaction with ethyl mercaptan furnished the tetrahydroquinazolinone **28** in 54% yield and the tetrahydrobenzodiazepinone **27** ($R = \text{SEt}$) in 19% yield.

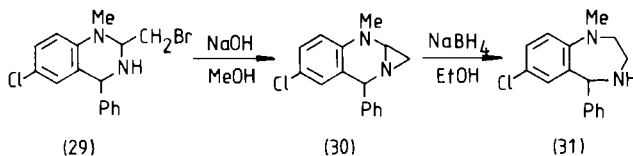


3. Physicochemical Properties

The following spectral data are available for cyclopropa[*e*]pyrrolo[1,2-*a*]-pyrimidines: UV and ^1H NMR³; and for azirino[1,2-*a*]quinazolines: UV,^{4,5} IR⁸ and ^1H NMR.^{4,5,8}

C. AZIRINO[2,1-*b*]QUINAZOLINES (RING SYSTEM TYPE III)

The first representative of ring system Type III was obtained by Sorrentino during the synthesis of 1,2,3,5-tetrahydro-3*H*-1,4-benzodiazepines.¹¹ Ring expansion of 2-halomethyl-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinazolines to 1,4-benzodiazepines involves the formation of azirino[2,1-*b*]quinazolines of type **30**. This step is followed by cleavage of the C—N bond of the aziridine ring by the action of sodium borohydride.



¹¹ P. D. Sorrentino, British Patent 1,279,842 [CA 77, 114442 (1972)].

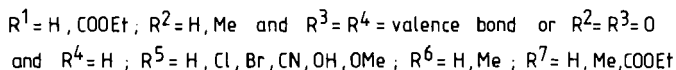
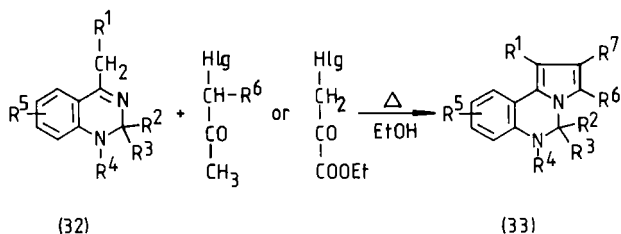
Cyclization of the 2-(bromomethyl)tetrahydroquinazoline **29** to the azirinoquinazoline **30** was effected with sodium hydroxide in aqueous methanol at room temperature.¹¹

III. Other Angular Annelated Ring Systems with Nitrogen Away from the Ring Angle (Type I)

A. SYNTHESSES

1. From Quinazolines

Bandurco and co-workers¹²⁻¹⁵ prepared a number of pyrrolo[1,2-*c*]quinazolines (**33**) by treating 4-methylquinazoline and its derivatives (**32**) with α -haloketones or α -halopyruvates in refluxing ethanol.



In the reaction of 4-methylquinazolin-2(1*H*)-ones (**34**) and α -chloroacetone, the two isomeric products **35** and **36** and the chlorine-containing by-product **38** were obtained.^{12,13} Compound **38** is formed as a result of a secondary reaction between the intermediate **37** and α -chloroacetone.

Lown and Matsumoto studied the reactions of a variety of heteroaromatic nitrogen compounds with diphenylcyclopropenone (**39**)¹⁶ and diphenylcyclopropenethione (**40**).¹⁷ Quinazoline with the cyclopropenone **39** gave the pyrrolo[1,2-*c*]quinazoline **41**, but reaction with thione **40** resulted in **42**, a product in which one molecule of the solvent methanol was also incorporated.

¹² V. T. Bandurco, E. M. Wong, S. D. Levine, and Z. G. Hajas, *J. Med. Chem.* **24**, 1455 (1981).

¹³ V. T. Bandurco and S. Levine, U.S. Patent 4,129,653 [CA **90**, 137861 (1979)].

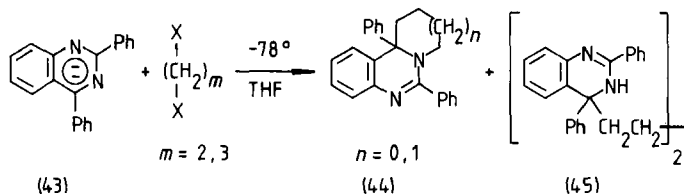
¹⁴ M. L. Cotter, V. Bandurco, E. Wong, and Z. G. Hajas, *J. Heterocycl. Chem.* **16**, 623 (1979).

¹⁵ M. L. Cotter, V. Bandurco, and E. Wong, *J. Heterocycl. Chem.* **16**, 1497 (1979).

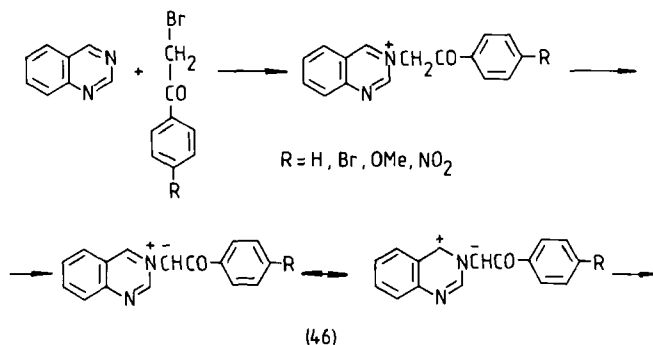
¹⁶ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **49**, 1165 (1971).

¹⁷ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **49**, 3119 (1971).

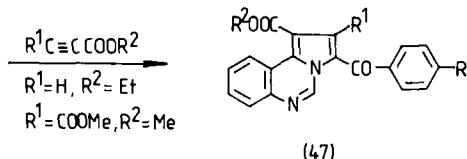
The dianion **43**, prepared from 2,4-diphenylquinazoline with sodium in tetrahydrofuran, was alkylated with 1, ω -dihaloalkanes ($m = 2, 3$) and gave the pyrrolo[1,2-*c*]quinazoline **44** ($n = 0$) and the pyrido[1,2-*c*]quinazoline **44**: ($n = 1$), respectively.¹⁸ Attempts to fuse a six-membered ring to the quinazoline ring by the use of 1,4-dibromobutane were less satisfactory.



Although the pyridoquinazoline **44** ($n = 1$) was obtained, competitive intermolecular alkylations also occurred and the dimeric product **45** and oligomeric materials too were formed.



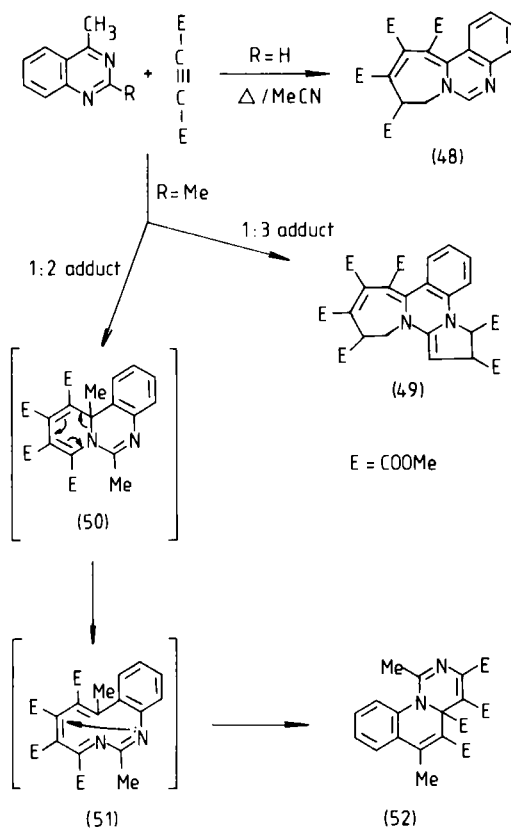
Reaction of quinazoline with phenacyl bromides and subsequently with dimethyl acetylenedicarboxylate or ethyl propiolate in propylene oxide at ambient temperature gave the pyrrolo[1,2-*c*]quinazolines **47**.¹⁹ The latter are formed in a [3 + 2] dipolar cycloaddition between the quinazolinium ylides **46**, generated *in situ*, and the acetylene derivatives.



¹⁸ J. G. Smith, J. M. Sheepy, and E. M. Levi, *J. Org. Chem.* **41**, 497 (1974).

¹⁹ E. Georgescu, I. Druta, and M. Petrovanu, *Rev. Roum. Chim.* **26**, 109 (1981) [*CA* **94**, 208802 (1981)].

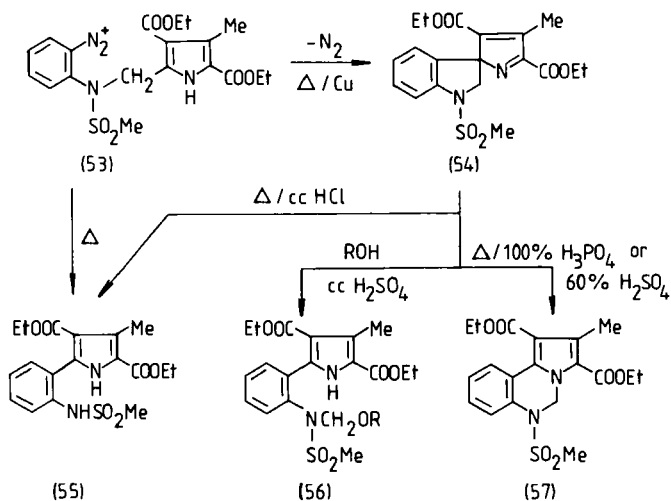
Acheson *et al.*²⁰ studied the formation of azepines by treating a number of nitrogen-containing heterocycles possessing activated methyl groups ortho to the nitrogen atom with dimethyl acetylenedicarboxylate. From 4-methylquinazoline the azepino[1,2-*c*]quinazoline **48** was obtained in 2.3% yield. 2,4-Dimethylquinazoline gave low yields of two products, the 2:1 adduct **52** and the 3:1 adduct **49**. The 3:1 adduct **49** proved to be a derivative of azepino[1,2-*c*]quinazoline, while the 2:1 adduct was identified as the pyrimido[3,4-*a*]quinoline **52**. The latter may have been obtained through the initial formation of the pyrido[1,2-*c*]quinazoline **50**, followed by valency tautomerism to yield **51** and cyclization at the alternative nitrogen atom.



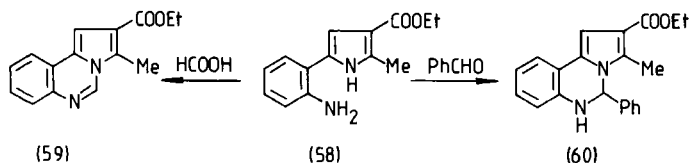
²⁰ R. M. Acheson, M. W. Foxton, and J. K. Stubbs, *J. Chem. Soc. C* 926 (1968).

2. Miscellaneous Syntheses

Copper-catalyzed decomposition of the diazonium chloride **53**, derived from the appropriate amine, gave the spiro compound **54** besides a few percent of the phenylpyrrole **55**.²¹ The phenylpyrrole **55** was obtained in high yield from the diazonium chloride **53** or from the spiro compound **54** on heating in hydrochloric acid. If the spiro derivative **54** was melted at 200°C or heated in 100% phosphoric acid or 60% sulfuric acid at 100°C, the pyrrolo[1,2-*c*]quinazoline **57** was formed, whereas in alcoholic solution, in the presence of a few drops of concentrated sulfuric acid, compound **56** was obtained.



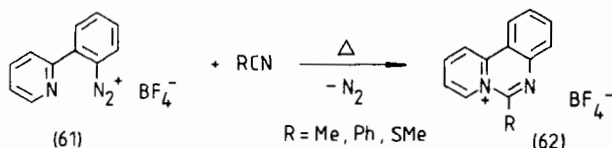
Ethyl 3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (**59**) and its 5-phenyl-5,6-dihydro derivative (**60**) were prepared by treating ethyl 5-(2-aminophenyl)-3-methylpyrrole-3-carboxylate (**58**) with formic acid and with benzaldehyde, respectively.²²



²¹ S. Beveridge and J. L. Huppatz, *Aust. J. Chem.* **23**, 781 (1970).

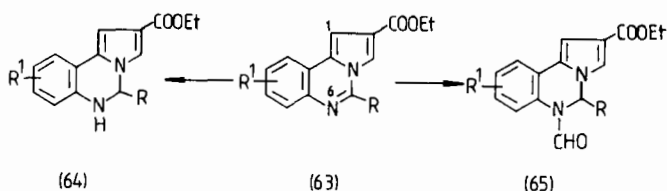
²² E. Ayello, *Atti Accad. Sci., Lett. Arti Palermo, Parte I* **30**, 237 (1969–1970) [*CA* **77**, 152110 (1972)].

The pyrido[1,2-*c*]quinazolinium-7 tetrafluoroborates **62** were obtained by treating 2-(2-pyridyl)benzenediazonium tetrafluoroborate (**61**) with nitriles at 80°C until nitrogen was no longer evolved.²³



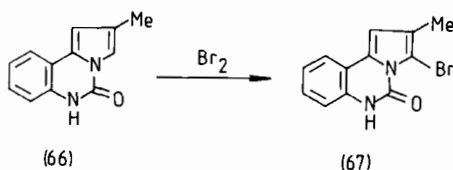
B. REACTIONS

Catalytic^{12,13} (H_2/PtO_2) or chemical^{13,15} (NaBH_3CN) reduction of the ethyl pyrrolo[1,2-*c*]quinazoline-2-carboxylates **63** affords the 5,6-dihydro derivatives **64**.



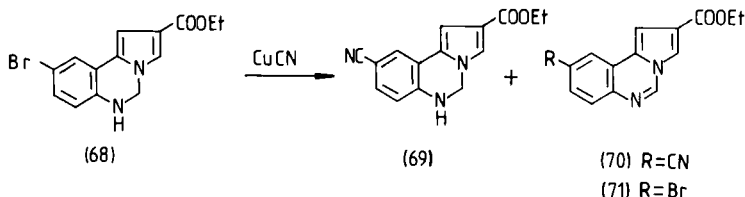
When lithium aluminum hydride was applied, besides reduction of the C-4—N-5 double bond, the ester group was converted to a hydroxymethyl group.^{12,13} By reaction with dry formic acid under reflux conditions, the pyrroloquinazoline-2-carboxylates **63** yielded the 6-formyl-5,6-dihydro derivatives **65**.^{12,13} The formyl group was transformed into a methyl group by diborane.^{12,13} The NH group of the dihydro derivatives **64** was acylated by ethyl chloroformate.^{13,15} Reaction with ethyl acrylate and acrylonitrile involved a Michael addition.^{12,13} The ethoxycarbonyl moiety in position 2 and on the side chain in position 6 was hydrolyzed to a carboxylic group by the action of potassium hydroxide in aqueous methanol and was reduced to a hydroxymethyl group by lithium aluminum hydride in ether.^{12,13}

2-Methylpyrrolo[1,2-*a*]quinazolin-5(6*H*)-one (**66**) with bromine in carbon tetrachloride at reflux temperature gave the 3-bromo compound **67**.^{12,13}

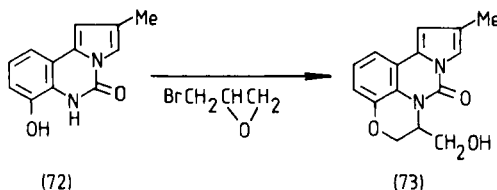


²³ R. R. Schmidt, German Patent 2,043,665 [CA 77, 34478 (1972)].

Ethyl 9-bromo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-2-carboxylate (**68**) reacted with copper cyanide in dimethylformamide to yield the 9-cyano-5,6-dihydro derivative **69** together with 9-cyanopyrroloquinazoline-2-carboxylate (**70**) and the 9-bromo-5,6-dehydro derivative **71**, isolated by column chromatography.^{12,13}



The 9-hydroxy derivative of the pyrroloquinazoline of type **66** was O-alkylated with epibromohydrin, and the epoxy ring was opened with isopropylamine in a pressure bottle under heating.¹² Reaction of 7-hydroxy-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (**72**) with epibromohydrin in the presence of sodium hydroxide gave the condensed oxazine derivative **73**.¹⁴



The 3-hydroxy group of the pyrrolo[1,2-*c*]quinazoline **41** was converted to a 3-ethoxy group by the action of triethyloxonium tetrafluoroborate.¹⁶

C. PHYSICOCHEMICAL PROPERTIES

The pyrrolo[1,2-*c*]quinazolines are characterized through their UV,^{16,21,24} IR,^{16,19,24} and ¹H-NMR^{12,16,17,20,21,24} spectra, the pyrido[1,2-*c*]quinazoline **44** (*n* = 1)¹⁸ through its UV, IR, and ¹H-NMR spectra, and the azepino[1,2-*c*]quinazoline **48** through its UV,²⁰ IR,²⁰ ¹H-NMR,²⁰ and mass spectra.²⁵

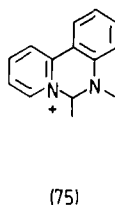
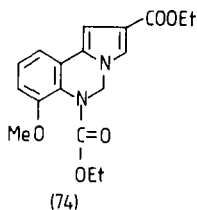
The 6-ethoxycarbonyl group in the pyrrolo[1,2-*c*]quinazoline-2-carboxylate **74** was demonstrated by NMR to experience an unusual steric barrier to free rotation about the N-6—C bond; this is due to the proximity of the

²⁴ J. G. Smith and J. M. Sheepy, *J. Heterocycl. Chem.* **12**, 231 (1975).

²⁵ R. M. Acheson, R. T. Aplin, and D. R. Harrison, *J. Chem. Soc. C*, 383 (1968).

7-methoxy group.¹⁵ Low-temperature NMR studies showed that the *exo* isomer predominated. The energy barrier was calculated from coalescence temperature data to be 13.9 kcal/mol.

Electronic spectral shifts induced in the model fragment **75** by the introduction of a dimethylamino or cyano group into different positions were computed by MO-LCAO methods.²⁶



D. APPLICATIONS

The pyrrolo[1,2-*c*]quinazolines **33** have been patented for their cardiovascular activities and as antiasthmatic agents.¹³ A structure-activity study was made to optimize the antihypertensive properties of these compounds in the spontaneously hypertensive rat.¹²

IV. Other Angular Annulated Ring Systems with Nitrogen in the Ring Angle (Type II)

A. SYNTHESSES

1. From Anthranilic Acid Derivatives and from Quinazolines

Amides and mono substituted amides of anthranilic acid react with γ - or δ -oxocarboxylic acids to give the pyrrolo- or pyrido[1,2-*a*]quinazolines **76** ($n = 0, 1$).²⁷⁻³⁰ Reactions were carried out under reflux in the presence of^{27,28} or without^{29,30} *p*-toluenesulfonic acid. Instead of the carboxylic acids, the esters can be applied.

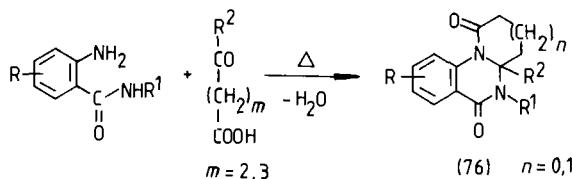
²⁶ J. Fabian, *Z. Chem.* **21**, 263 (1981).

²⁷ W. J. Houlihan, U.S. Patent 3,441,566 [CA **71**, 70630 (1969)].

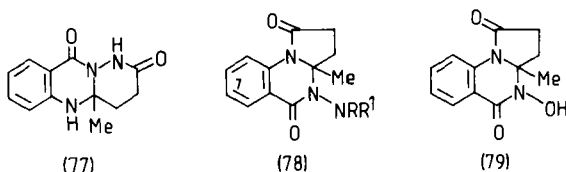
²⁸ E. H. Wolf and B. J. Duffy, U.S. Patent 3,883,524 [CA **83**, 131624 (1975)].

²⁹ P. Aeberli and W. J. Houlihan, *J. Org. Chem.* **33**, 2402 (1968).

³⁰ F. Gatta and R. Landi Vittory, *Gazz. Chim. Ital.* **99**, 715 (1969).

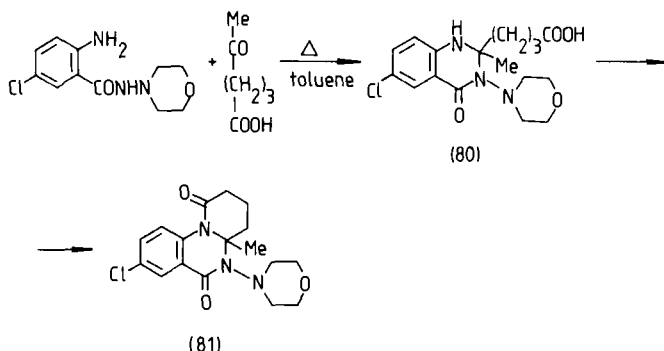


With levulinic acid, anthraniloyl hydrazide gave the pyridazino-[3,2-*b*]quinazoline **77**,³¹⁻³³ whereas the N^2 -disubstituted hydrazides formed the pyrrolo[1,2-*a*]quinazoline-1,5-diones **78**.^{28,31,32}



From the hydroxamic acid derivative of anthranilic acid, Gherardini and Pestellini obtained an N -hydroxy derivative (**79**).³¹

In some cases intermediates could also be isolated.^{28,34} Wolf and Duffy²⁸ treated 2-amino-5-chloro- N -morpholinobenzamide with 5-oxohexanoic acid in toluene and isolated the tetrahydroquinazolinone **80**, which then was cyclized in a mixture of *o*-dichlorobenzene and xylene to the pyrido[1,2-*a*]quinazoline **81**.



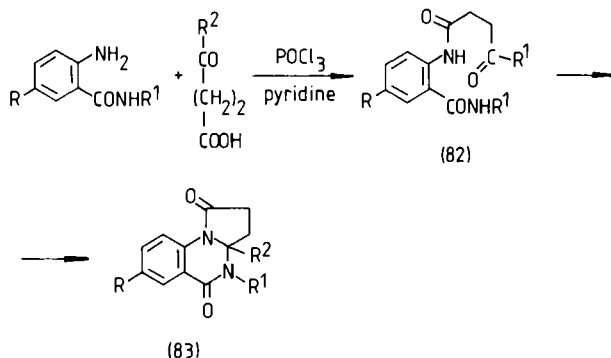
³¹ F. K. Kirchner and A. W. Zalay, U.S. Patent 3,375,250 [CA **69**, 52170 (1968)].

³² F. K. Kirchner and A. W. Zalay, U.S. Patent 3,843,654 [CA **82**, 112098 (1975)].

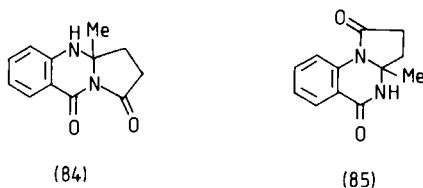
³³ M. Ghelardoni and V. Pestellini, *Ann. Chim. (Rome)* **64**, 445 (1974).

³⁴ C. S. Rao, A. D. Pandya, P. N. Mody, and M. P. Dave, *Indian J. Chem., Sec. B* **14B** 705 (1976).

Rao *et al.*³⁴ treated anthranilamides with γ -oxocarboxylic acids in pyridine at 45–50°C in the presence of phosphoryl chloride and obtained the diamides (82), which cyclized to the pyrrolo[1,2-*a*]quinazolines 83 in refluxing benzene or toluene.



Westphal and Stroh³⁵ originally thought that the product obtained in the reaction of anthranilic acid and levulinic acid was the linearly annelated compound 84. The pyrrolo[1,2-*a*]quinazoline-1,5-dione structure 85 was later elucidated by Yamato and Takeuchi.³⁶



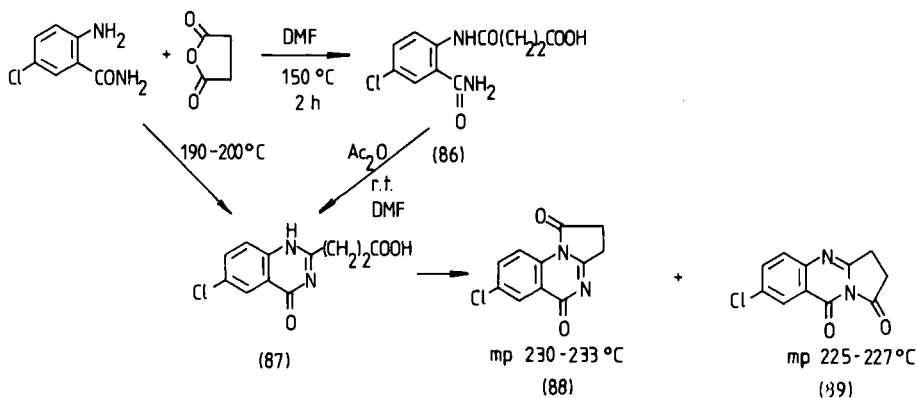
From 5-chloroanthranilamide and succinic anhydride, Bell *et al.*^{37,38} prepared the diamide 86 and cyclized this in acetic anhydride at room temperature to the quinazoline 87. When heated in dimethylformamide and acetic anhydride on a water bath for 25 min, the quinazoline afforded the pyrrolo[1,2-*a*]quinazoline 88, while on reaction for 45 min a 2:1 mixture of 88 and the isomeric pyrrolo[2,1-*b*]quinazoline 89 was formed. The yield of the linearly fused product 89 rose with increasing reaction time and temperature.³⁸ The quinazolinepropionic acid 87 was also generated directly from 5-chloroanthranilamide and succinic anhydride.

³⁵ G. Westphal and H. H. Stroh, *Z. Chem.* **7**, 456 (1967).

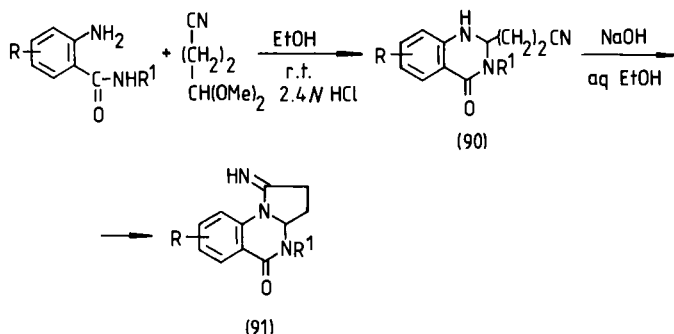
³⁶ M. Yamato and Y. Takeuchi, *Chem. Pharm. Bull.* **30**, 1036 (1982).

³⁷ S. C. Bell and G. Conklin, *J. Heterocycl. Chem.* **5**, 179 (1968).

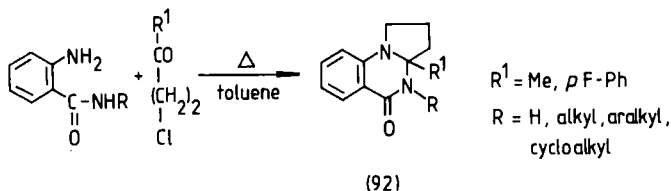
³⁸ S. C. Bell and P. H. L. Wei, U.S. Patent 3,475,432 [*CA* **71**, 124487 (1969)].



Bell and Concklin prepared the 1-aminopyrrolo[1,2-*a*]quinazolines **91** from anthranilamide and 4,4-dimethoxybutyronitrile either directly, by heating them in dimethoxyethane under reflux conditions in the presence of hydrochloric acid,³⁷ or through the quinazolinepropionitriles **90**, which cyclize when heated in aqueous ethanolic sodium hydroxide solution.³⁹



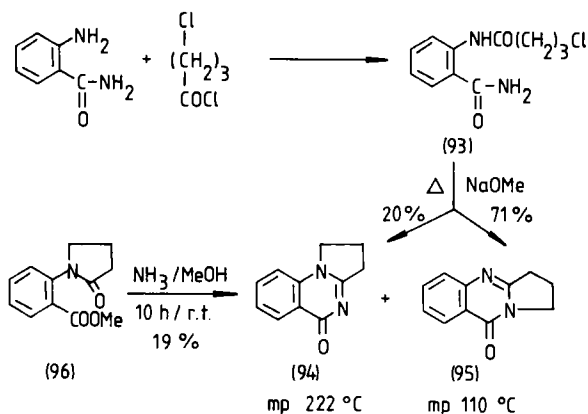
Reaction of the anthranilamides with β -chloro ketones gave the pyrrolo[1,2-*a*]quinazolines **92**.^{30,34,40}



³⁹ S. C. Bell and G. T. Concklin, U.S. Patent 3,707,468 [CA 78, 72188 (1973)].

⁴⁰ R. Landi Vittori and F. Gatta, *Gazz. Chim. Ital.* **99**, 59 (1969).

The diamide **93**, prepared from anthranilamide and γ -chlorobutyryl chloride, was cyclized in the presence of sodium methoxide by Landi Vittory and Gatta.⁴⁰ The reaction yielded a mixture of the linearly and angularly fused tricyclic compounds **95** and **94**. The pyrrolo[1,2-*a*]quinazoline **94** was also prepared from the ester **96** by treatment with methanolic ammonia.⁴⁰



Taylor and Shvo⁴¹ obtained a good yield of the pyrrolo[1,2-*a*]quinazoline **94** from anthranilonitrile and γ -chlorobutyryl chloride. Ring closure was effected with dry gaseous hydrogen chloride.

Arya *et al.*⁴² prepared the pyrrolo[1,2-*a*]quinazoline **94** directly from anthranilamide and butyrolactone, in a yield of 45%, by reaction in acetic acid in the presence of boron trifluoride etherate. The 7-chloro and 8-chloro derivatives of **94** were prepared similarly. The 8-chloro derivative of **94** was also synthesized from methyl 4-chloroanthranilate and γ -chlorobutyronitrile.⁴²

A mixture of the angularly fused tricycles **98** and the linearly fused tricycles **99** resulted when Möhrle and Seidel⁴³ heated anthranilamide with the lactone **97** in a sealed tube at 270°C.

Kovtunenکو *et al.*⁴⁴ synthesized the pyrrolo- and pyrido[1,2-*a*]quinazolines **98** in 37–78% yield from alkyl anthranilates and ω -halobutyronitriles or ω -halovaleronitriles at 140°C.

Böhme and Böing⁴⁵ cyclized the tetrahydroquinazolines (**100**) with alkali

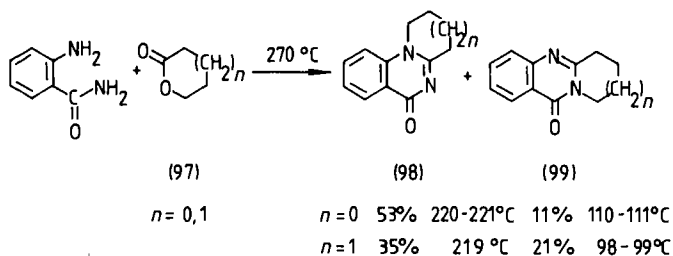
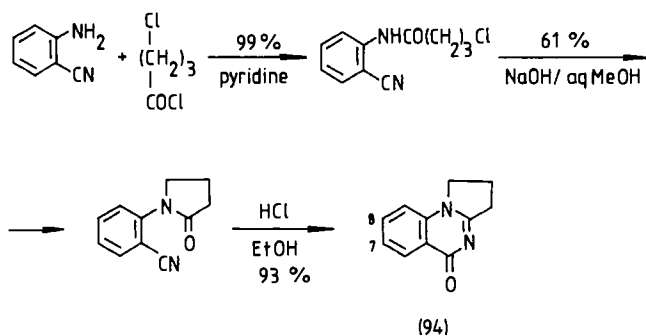
⁴¹ E. C. Taylor and Y. Shvo, *J. Org. Chem.* **33**, 1719 (1968).

⁴² V. P. Arya, K. G. Dave, V. G. Khadse, and S. J. Shenoy, *Indian J. Chem., Sect. B* **14B**, 879 (1976).

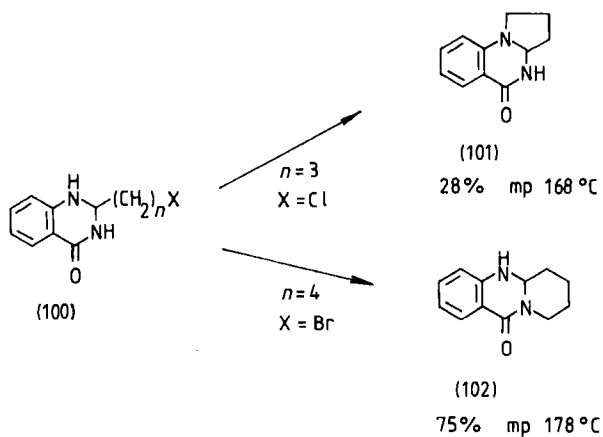
⁴³ H. Möhrle and M. Seidel, *Chem. Ber.* **106**, 1595 (1973).

⁴⁴ V. A. Kovtunenکو, A. K. Tytlin, and L. V. Soloshonok, *Khim. Geterosikl. Soedin.*, 1427 (1979) [*CA* **92**, 110954 (1980)].

⁴⁵ H. Böhme and H. Böing, *Arch. Pharm. (Weinheim, Ger.)* **294**, 556 (1961).

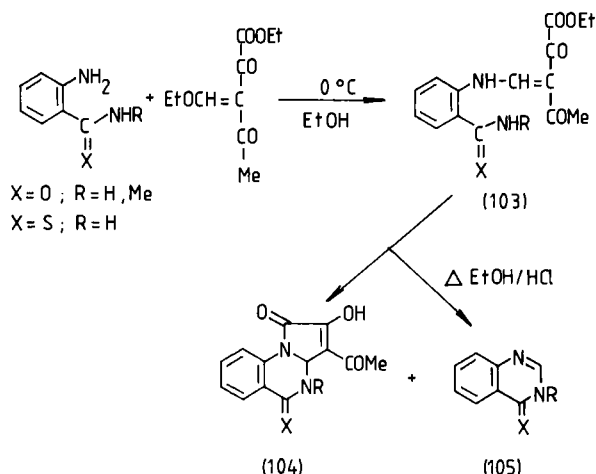


metal hydroxides. Compound **100** ($n = 3$) yielded the angularly fused product **101**, whereas the homolog **100** ($n = 4$) gave the linearly annelated **102**.



Landi Vittory and Gatta⁴⁶ cyclized 2-(3-hydroxypropyl)-3-methyl-1,2,3,4-tetrahydroquinazolin-4-one to the 4-methyl derivative of **101** with thionyl chloride.

Kurihare *et al.*^{47,48} found that condensation of anthranilamides and anthraniloyl thioamides with ethyl 3-ethoxymethylene-2,4-dioxovalerate and cyclization of the resulting **103** in ethanol in the presence of a catalytic amount of concentrated hydrochloric acid led to a mixture of the pyrrolo[1,2-*a*]quinazolines **104** and the quinazolines **105**. The reaction was also performed without isolation of **103**.



It was reported by Babichev and Volovenko⁴⁹ that the reaction of methyl anthranilate and the 4-chloro-3-oxobutyronitriles **106** afforded the pyrrolo[1,2-*a*]quinazolines **107**. With potassium ethoxide in ethanol Brodrick and Wibberley⁵⁰ transformed the succinonitrile **108**, prepared from methyl anthranilate and 2-formylsuccinonitrile, into the pyrrolo[1,2-*a*]quinazoline **109** in 95% yield.

Zimmermann and Eger⁵¹ treated methyl anthranilate and anthranilonitrile first with 3-hydroxy-2-butanone in toluene, in the presence of a catalytic

⁴⁶ R. Landi Vittory and F. Gatta, *Farmaco, Ed. Sci.* **27**, 208 (1972).

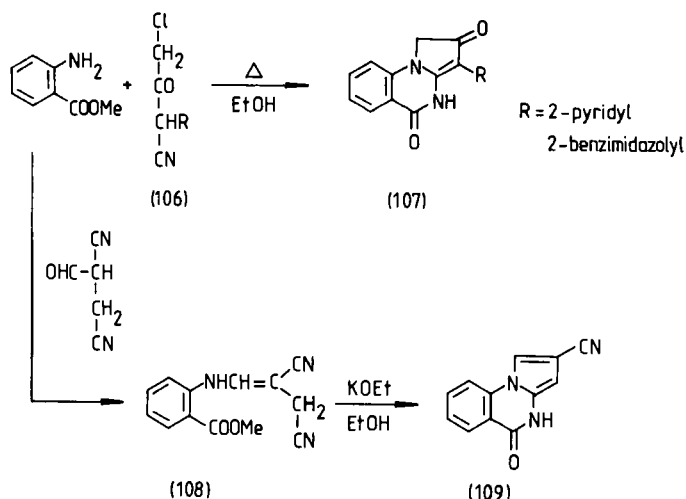
⁴⁷ T. Kurihara and Y. Sakamoto, *Heterocycles* **9**, 1729 (1978).

⁴⁸ T. Kurihara, T. Tani, and Y. Sakamoto, *J. Heterocycl. Chem.* **17**, 945 (1980).

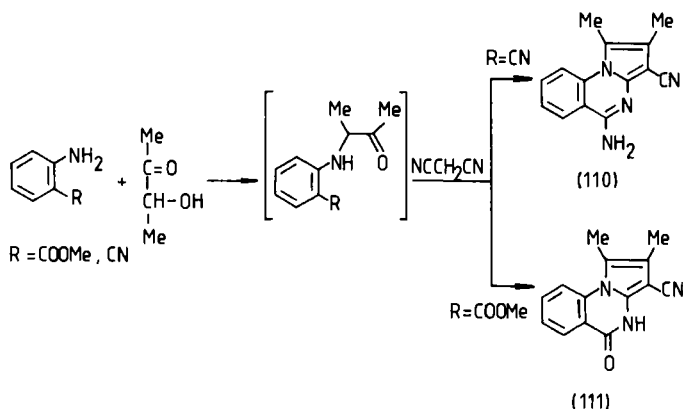
⁴⁹ F. S. Babichev and Yu. M. Volovenko, *Ukr. Khim. Zh. (Russ. Ed.)* **43**, 711 (1977) [*CA* **87**, 184451 (1977)].

⁵⁰ A. Brodrick and D. G. Wibberley, *J. C. S. Perkin I.* 1910 (1975).

⁵¹ W. Zimmermann and K. Eger, *Arch. Pharm. (Weinheim, Ger.)* **312**, 552 (1979).



amount of *p*-toluenesulfonic acid, then with malononitrile, and obtained the pyrrolo[1,2-*a*]quinazolinones **110** and **111**.



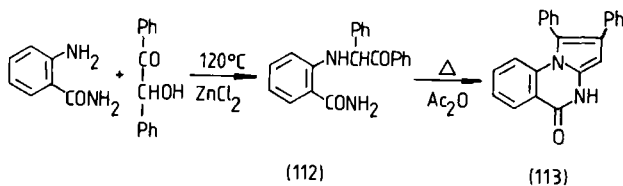
Kato and co-workers⁵² reported that on heating of the amide **112**, prepared from anthranilamide and benzoin in acetic acid, the pyrrolo[1,2-*a*]quinazoline **113** and anthranilonitrile were produced in 64 and 34% yields, respectively.

Suesse and Johne^{53,54} prepared the pyrrolo[1,2-*a*]quinazolinones **115**

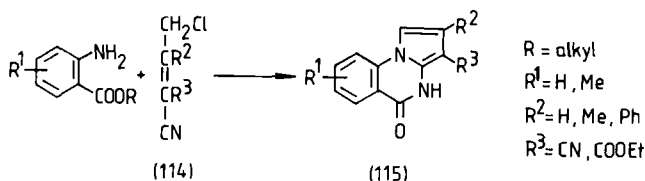
⁵² J. Horiuchi, M. Yamoto, N. Katagiri, and T. Kato, *Heterocycles* **19**, 249 (1982).

⁵³ M. Suesse and S. Johne, German (East) Patent 142,337 [*CA* **94**, 175162 (1981)].

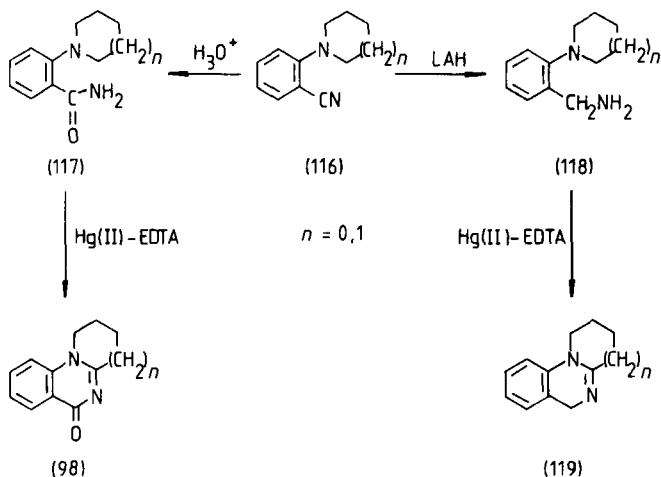
⁵⁴ M. Suesse and S. Johne, *J. Prakt. Chem.* **323**, 647 (1981).



from alkyl anthranilates and γ -halocrotononitriles **114** in the presence of triethylamine or pyridine.



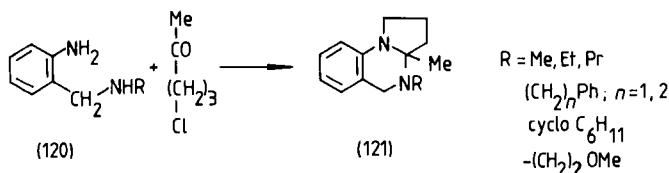
Möhrle *et al.* obtained the amides **117**⁵⁵ and benzylamines **118**⁵⁶ from benzonitriles **116** and oxidized them with mercuric acetate-EDTA reagent to the tricyclic compounds **98** and **119**, respectively.



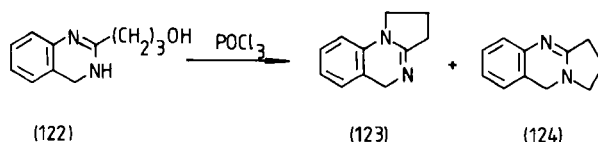
The hexahydropyrrolo[1,2-*a*]quinazolines **121** were prepared by Gatta and Landi Vittori³⁰ by treating 2-aminobenzylamines (**120**) with 5-chloro-2-pentanone.

⁵⁵ H. Möhrle and H.-J. Hemmerling, *Arch. Pharm. (Weinheim, Ger.)* **311**, 586 (1978).

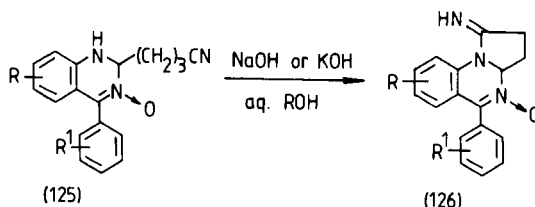
⁵⁶ H. Möhrle and J. Gerloff, *Arch. Pharm. (Weinheim, Ger.)* **312**, 838 (1979).



Jen *et al.*⁵⁷ obtained a 1 : 2 mixture of the pyrrolo[1,2-*a*]quinazoline **123** and the pyrrolo[2,1-*b*]quinazoline **124** from the reaction of 2-(3-hydroxypropyl)-3,4-dihydroquinazoline (**122**) with phosphoryl chloride under a nitrogen atmosphere.



The quinazolinepropionitrile 3-oxides **125** were cyclized with alkali metal hydroxide in aqueous alcohol to the pyrrolo[1,2-*a*]pyrimidine 4-oxides **126**.⁵⁸



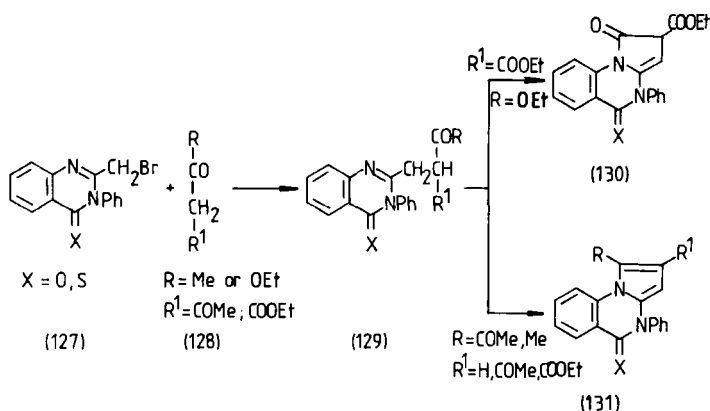
Sinha and co-workers^{59,60} reported that the reaction of the 3-bromomethylquinazolines **127** and CH acid compounds **128** gave rise to **129**, which were converted by heating in 2 *N* sulfuric acid or in polyphosphoric acid to the pyrrolo[1,2-*a*]quinazolines **130** and **131**. Reaction with diethyl malonate afforded the 1-oxopyrrolo[1,2-*a*]quinazolines **130**, whereas other CH acid compounds (**128**) gave the pyrrolo[1,2-*a*]quinazolines **131**. When **129** (R = Me, R¹ = COMe, X = O) was heated in polyphosphoric acid, the ring closure reaction was accompanied by deacetylation and led to the pyrrolo[1,2-*a*]quinazoline **131** (R = COMe, R¹ = H, X = O). Ring closure did not occur in acetic anhydride.⁵⁹

⁵⁷ T. Jen, B. Dienel, F. Dowalo, H. Van Hoveen, P. Bender, and B. Loev, *J. Med. Chem.* **16**, 633 (1973).

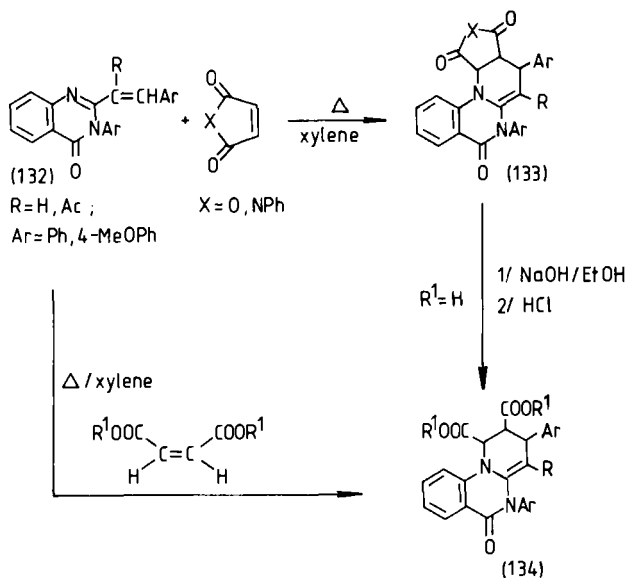
⁵⁸ S. C. Bell, U.S. Patent 3,506,663 [CA 73, 25511 (1970)].

⁵⁹ B. D. Singh and S. K. P. Sinha, *J. Indian Chem. Soc.* **48**, 743 (1971).

⁶⁰ M. P. Thakur and S. K. P. Sinha, *J. Indian Chem. Soc.* **49**, 1185 (1972).



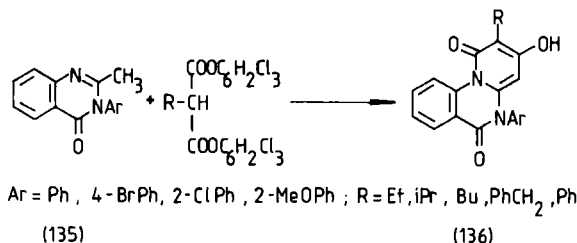
Egyptian researchers^{61,62} treated the 2-styryl-4-quinazolinones **132** with maleic anhydride and *N*-phenylmaleimide and obtained the Diels–Alder adducts **133**. The latter were hydrolyzed with alcoholic sodium hydroxide to the pyrido[1,2-*a*]quinazoline-1,2-dicarboxylic acids **134** ($R^1 = \text{H}$). The dicarboxylic acids **134** ($R^1 = \text{H}$) and their diesters ($R^1 = \text{Et}$) were also obtained in the reaction of the 2-styryl-4-quinazolinones **132** with maleic acid or diethyl maleate.



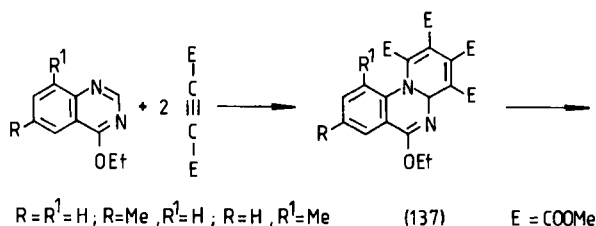
⁶¹ A. Sammour, T. Zimaity, and M. A. Abdo, *Egypt. J. Chem.* **16**, 215 (1973) [*CA* **81**, 152159 (1974)].

⁶² M. A. Elkasaby and N. A. Noureldin, *Indian J. Chem., Sect. B* **20B**, 290 (1981).

By treating bis-(2,4,6-trichlorophenyl) malonates with 2-methylquinazolinones (135), Kappe and co-workers⁶³ obtained the pyrido[1,2-*a*]quinazolines 136.



Acheson and co-workers⁶⁴⁻⁶⁶ studied the reaction of 4-ethoxyquinazolines and dimethyl acetylenedicarboxylate. Whereas cycloaddition of 4-ethoxyquinazoline and its 6-methyl derivative in refluxing acetonitrile gave the pyrido[1,2-*a*]quinazolines 137 (R = H, Me, R¹ = H),^{64,65} 4-ethoxy-8-methylquinazoline did not react under similar conditions, presumably because of the steric effect of the methyl group hindering electrophilic attack at the nitrogen.⁶⁴ However, when the reaction was carried out for 1 week at 10 kbar in methylene chloride at room temperature, the pyrido[1,2-*a*]quinazoline 138 (R = H, R¹ = Me) was obtained in 34% yield.⁶⁶ In this case too, the pyrido[1,2-*a*]quinazoline 137 (R = H, R¹ = Me) was formed in the first step and was then transformed into the isomeric compound 138 (R = H, R¹ = Me). A similar rearrangement occurred with the pyrido[1,2-*a*]quinazolines 137 (R = H, Me, R¹ = H) in the presence of traces of acid.^{64,65}

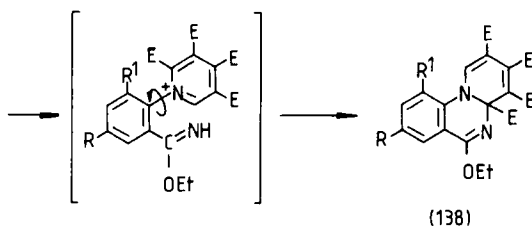


⁶³ F. S. G. Soliman, W. Stadlbauer, and T. Kappe, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **36B**, 252 (1981).

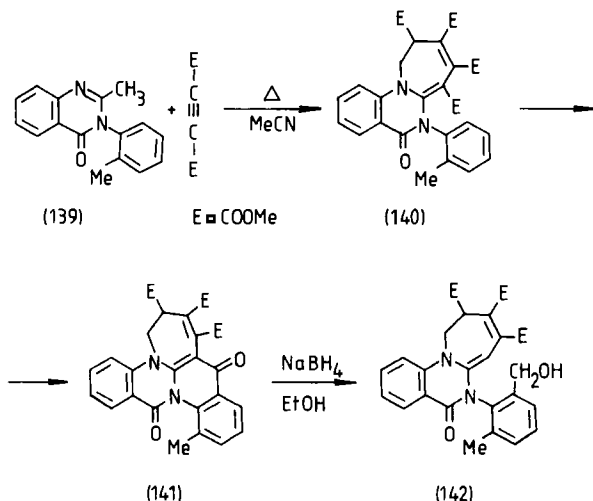
⁶⁴ P. J. Abbott, R. M. Acheson, M. Y. Kornilov, and J. K. Stubbs, *J. C. S. Perkin I*, 2322 (1975).

⁶⁵ R. M. Acheson, P. J. Abbott, J. K. Stubbs, and M. Yu. Kornilov, *Khim. Geterotsikl. Soedin.*, 1701 (1975) [*CA* **84**, 150043 (1976)].

⁶⁶ K. Matsumoto, S. Nakamura, and R. M. Acheson, *Heterocycles* **14**, 1959 (1980).



Taylor *et al.*⁶⁷ reported that reaction of the hypnotic agent methaqualone (139) with dimethyl acetylenedicarboxylate gave rise to the azepino[1,2-*a*]-quinazoline 140, which was converted in polyphosphoric acid at 140°C to the pentacyclic derivative 141. Reduction of 141 with sodium borohydride gave the azepino[1,2-*a*]-quinazoline 142.



2. Miscellaneous Syntheses

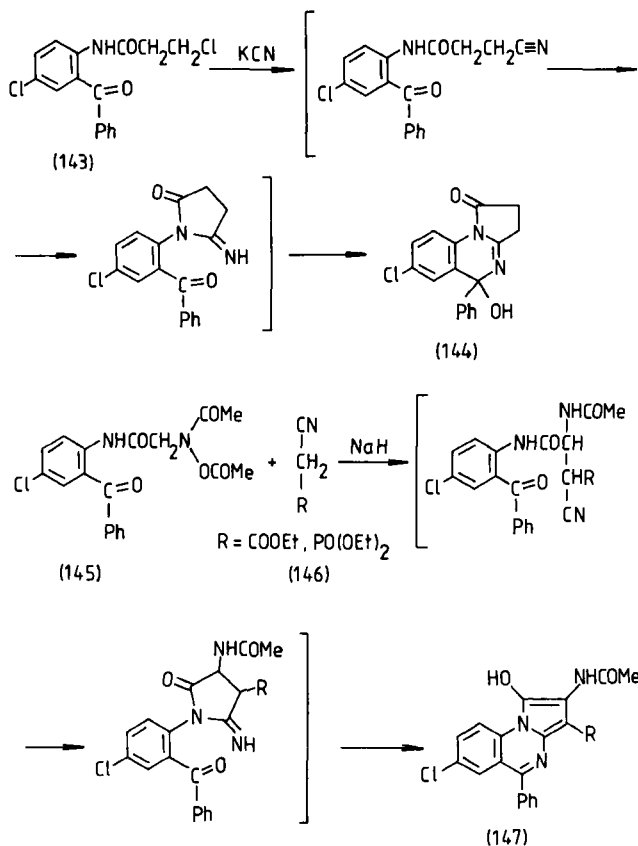
By treating the propionanilide 143 with potassium cyanide in refluxing aqueous dimethoxyethane, Bell and Wei^{68,69} obtained the 1-oxopyrrolo-[1,2-*a*]quinazoline 144. Reaction of the acetanilide 145 with CH acid compounds 146 in dimethylformamide in the presence of sodium hydride yielded the pyrrolo[1,2-*a*]quinazoline 147.^{68,70}

⁶⁷ J. B. Taylor, D. R. Harrison, and F. Fried, *J. Heterocycl. Chem.* **9**, 1227 (1972).

⁶⁸ S. C. Bell and P. H. L. Wei, *J. Heterocycl. Chem.* **5**, 185 (1968).

⁶⁹ S. C. Bell and P. H. L. Wei, U.S. Patent 3,595,861 [*CA* **75**, 98585 (1971)].

⁷⁰ S. C. Bell, U.S. Patent 3,459,754 [*CA* **71**, 81407 (1969)].



Garcia *et al.*⁷¹ cyclized the anti oxime **148** to the pyrrolo[1,2-*a*]quinoline 4-oxide **149** by use of one molar equivalent of bromine, and to the pyrrolo[1,2-*a*]quinazoline 4-oxide **150** with formaldehyde in acetic acid.

Ishikawa *et al.*⁷² prepared the oximes **152** by treating the ketones **151** with hydroxylamine hydrochloride in refluxing ethanol in the presence of pyridine. The oximes **152** were then cyclized in aqueous ethanol at room temperature in the presence of sodium hydroxide and Raney nickel to afford the angularly annelated tricycles **153**.

The 1-oxypyrrolo[1,2-*a*]quinazoline **155** was obtained by Juneja *et al.*⁷³ on heating of the succinic acid derivative **154** in acetic acid.

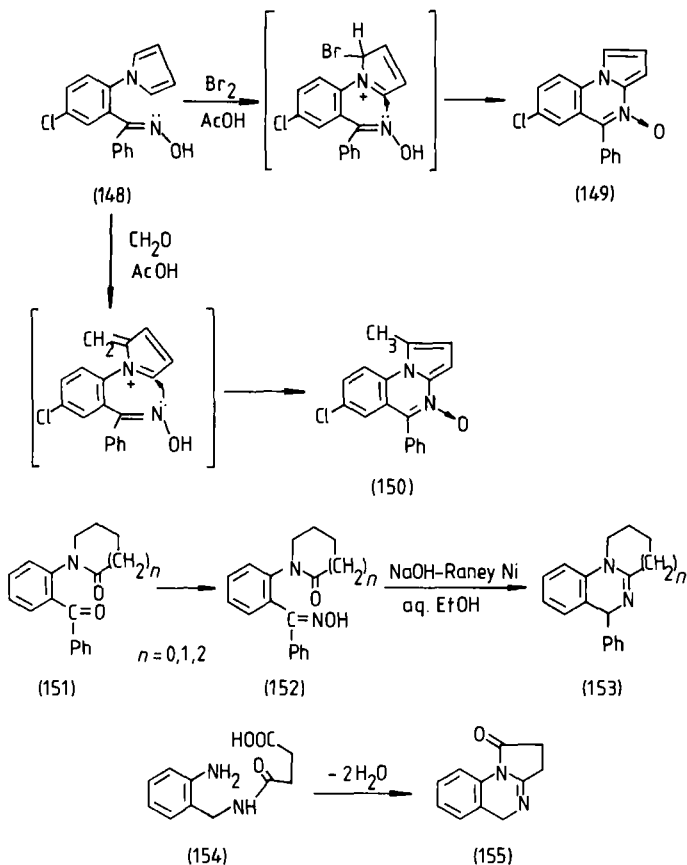
It was found by Gupta *et al.*⁷⁴ that reaction of 2-aminopyridine and methyl

⁷¹ E. G. Garcia, J. G. Riley, and R. I. Fryer, *J. Org. Chem.* **33**, 1359 (1968).

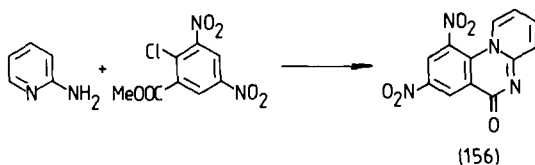
⁷² F. Ishikawa, A. Kosasayama, and K. Abiko, Japan Kokai 78/77,076 [*CA* **89**, 197584 (1978)].

⁷³ H. R. Juneja, K. S. Narang, and J. N. Ray, *J. Chem. Soc.*, 1277 (1935).

⁷⁴ C. M. Gupta, A. P. Bhaduri, and N. M. Khanna, *Indian J. Chem.* **6**, 758 (1968).

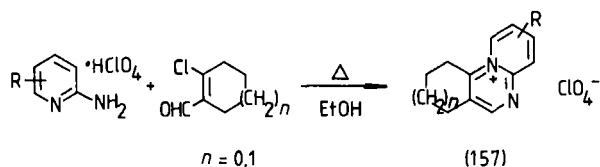


2-chloro-3,5-dinitrobenzoate in refluxing ethanol in the presence of anhydrous sodium acetate yielded the pyrido[1,2-*a*]quinazoline **156**.

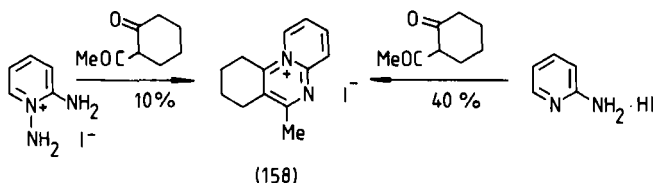


Chuiguk and Oksanich⁷⁵ described the reaction of 2-aminopyridinium perchlorates and 1-formyl-2-chlorocycloalkenes in refluxing ethanol, leading to the tricyclic products **157**.

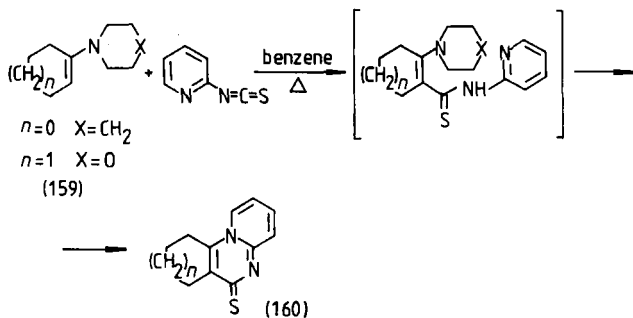
⁷⁵ V. A. Chuiguk and V. V. Oksanich, *Khim. Geterosikl. Soedin.*, 242 (1973) [*CA* **79**, 6745 (1973)].



Potts *et al.*⁷⁶ treated 1,2-diaminopyridinium iodide with 2-acetylcyclohexanone in refluxing pyridine and obtained the pyrido[1,2-*a*]quinazolinium iodide **158** in 10% yield. When 2-aminopyridinium iodide was used instead of 1,2-diaminopyridinium iodide, the yield of **158** was higher.



Marchalin *et al.*⁷⁷ synthesized the homologous tricyclic derivatives **160** ($n = 0, 1$) in good yields by treating 2-pyridyl isothiocyanate with the enamines **159** in boiling benzene.



B. REACTIONS

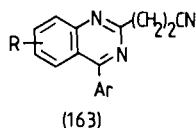
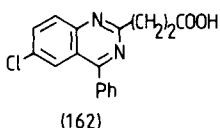
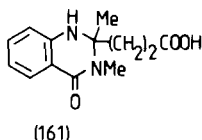
1. Hydrolysis and Ring Cleavage

Alkaline or acidic hydrolysis of the pyrrolo[1,2-*a*]quinazolines **83** ($R = H$, $R^1 = R^2 = Me$), **88**, and **144** gave the corresponding 2-quinazolinepro-

⁷⁶ K. T. Potts, R. Dugas, and C. R. Surapaneni, *J. Heterocycl. Chem.* **10**, 821 (1973).

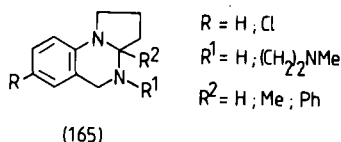
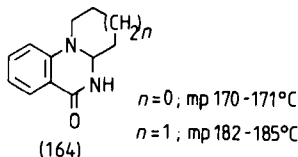
⁷⁷ M. Marchalin, J. Svetlik, and A. Martvon, *Collect. Czech. Chem. Commun.* **46**, 2428 (1981).

pionic acids **161**, **87**, and **162**.^{36,68} When the 1-iminotetrahydropyrrolo-[1,2-*a*]quinazoline 4-oxides **126** were heated in a carboxylic acid anhydride or in a mixture of carboxylic acid anhydride and carboxylic acid, the 2-quinazolinepropionitriles **163** were obtained.⁵⁸



2. Reduction, Oxidation

Reduction of the pyrrolo- and pyrido[2,1-*a*]quinazolinones **98** ($n = 0, 1$) with sodium borohydride led to the hexahydro derivatives **164**.^{40,42,78} Lithium aluminum hydride reduction of the tetrahydropyrrolo[1,2-*a*]quinazolin-5-one **94**⁴⁰ and the hexahydropyrrolo[1,2-*a*]quinazolin-5-ones **92** and **101**^{30,40,79} and -1,5-diones **83** ($R = H, Cl$; $R^1 = H$; $R^2 = H, Ph$)^{37,80} afforded the hexahydropyrrolo[1,2-*a*]quinazolines **165**. The hexahydropyrrolo[1,2-*a*]quinazoline **165** ($R = R^1 = H$) was also prepared by the electrolytic reduction of the tetrahydropyrrolo[1,2-*a*]quinazolin-1-one **153**.⁷³



The pyrrolo[1,2-*a*]quinazoline 4-oxides **149** and **150** were deoxygenated by hydrogen over Raney nickel.⁷¹ Upon reduction in methanol over palladium on carbon, the 5-chloropyrrolo[1,2-*a*]quinazoline **166** was transformed into the tetrahydropyrrolo[1,2-*a*]quinazolin-5-one **167**. If magnesium oxide was also present, **166** was converted to the pyrrolo[1,2-*a*]quinazoline **168**.⁵² The 7-nitro group in compounds of type **78** was hydrogenated to an amino group over palladium on carbon.²⁸

Oxidation of the pyrido[1,2-*a*]quinazolinium iodide **158** with potassium permanganate yielded 2-acetamidopyridine.⁷⁶

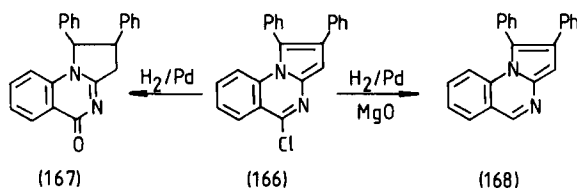
The pyrrolo- and pyrido[1,2-*a*]quinazolinones **164** ($n = 0, 1$) were oxidized with mercuric acetate–EDTA complex to **98** ($n = 0, 1$).⁸¹

⁷⁸ H. Möhrle and Ch. M. Seidel, *Arch. Pharm. (Weinheim, Ger.)* **309**, 503 (1976).

⁷⁹ J. Bernstein and E. R. Spitzmiller, U.S. Patent 3,271,400 [*CA* **65**, 18601 (1966)].

⁸⁰ P. Aaberli and W. Houlihan, *J. Heterocycl. Chem.* **15**, 1141 (1978).

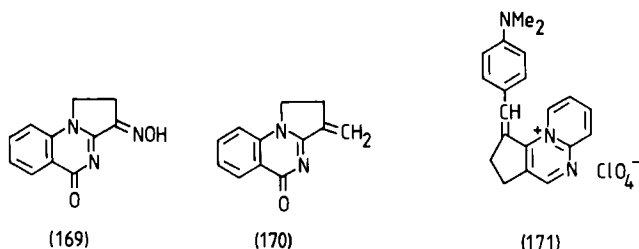
⁸¹ H. Möhrle and Ch. M. Seidel, *Arch. Pharm. (Weinheim, Ger.)* **309**, 572 (1976).



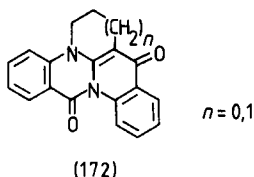
The tetrahydropyrrolo[1,2-*a*]quinazolin-5-one **94** was produced in the oxidation of the tetrahydropyrrolo[1,2-*a*]quinazoline **123** by air bubbles in boiling phosphoryl chloride.⁵⁷

3. Active Methylene Group Reactions

Treatment of the tetrahydropyrrolo[1,2-*a*]quinazolin-5-one **94** with isoamyl nitrite gave the oxime **169**, while reaction with bis(dimethylamino)methane in acetic anhydride afforded the exomethylene compound **170**.⁴¹ Condensation of the cyclopenta[*e*]pyrido[1,2-*a*]pyrimidinium perchlorate **157** ($n = 1$, $R = \text{H}$) with *p*-dimethylaminobenzaldehyde gave the methine dye **171**.⁷⁵



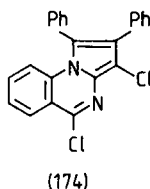
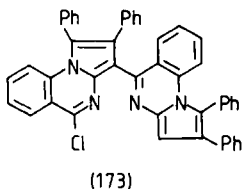
Möhrle and Seidel obtained the pentacyclic compounds **172** when **98** was treated with methyl anthranilate at 270°C in a sealed tube.⁴³



4. Miscellaneous Reactions

On the action of phosphoryl chloride the 4,5-dihydropyrrolo[1,2-*a*]quinazolin-5-one **113** gave the 5-chloro derivative **166** and the bis derivative **173**

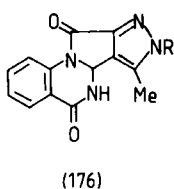
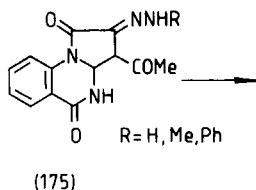
in 75 and 20% yields, respectively.⁵² If chlorination was carried out with phosphorus pentachloride, the 3,5-dichloro-1,2-diphenylpyrrolo[1,2-*a*]pyrimidine **174** was obtained.⁵²



The unsubstituted N-4 atom of the pyrrolo[1,2-*a*]quinazolines **83** ($R^1 = H$),^{34,37,39} **101**,^{40,79} and **165** ($R^1 = H$)⁴⁰ could be alkylated, while that of **83** ($R^1 = H$)³⁶ could also be acylated. The imino group of compounds **91**^{37,39} and **126**⁵⁸ was hydrolyzed to an oxo group, and that in **91**^{37,39} was acylated with acetic anhydride and chloroacetic anhydride.

The hydroxyl group in position 4 of **79** was acylated with acetic anhydride.³³

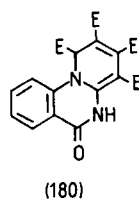
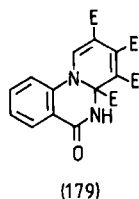
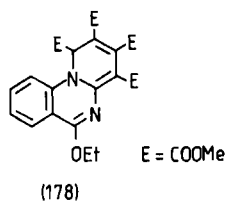
The 2-hydroxy group in the pyrrolo[1,2-*a*]quinazoline **104** was alkylated with diazomethane^{47,48} and underwent condensation with aniline^{47,48} and hydrazines.⁴⁸ The hydrazones **175** were cyclized to the pyrazolo[4,3-*c*]quinazolo[1,2-*a*]pyrroles **176**.⁴⁸



Allylation of the pyrido[1,2-*a*]quinazoline-1,5-dione **136** ($R = Ph$, $Ar = Ph$) with allyl bromide afforded the corresponding 3-allyloxy derivatives.⁶³ The hydroxymethylene group of the azepino[1,2-*a*]quinazolinone **142** was acetylated with acetyl chloride.⁶⁷ When the cyclopenta[*e*]pyrido[1,2-*a*]pyrimidine-4-thione **160** ($n = 0$) was treated with methyl iodide, a quaternary salt (**177**) was obtained.⁷⁷

The 3-ester group of the pyrrolo[1,2-*a*]quinazolines **115** ($R^3 = COOEt$) was transformed by hydrazinolysis.⁵⁴ The carboxylic groups of the pyrido[1,2-*a*]quinazolines **134** ($R^1 = H$) were esterified in ethanolic solution in the presence of dry hydrogen chloride.^{61,62}

Photolysis of the pyrido[1,2-*a*]quinazoline **137** ($R = R^1 = H$) in methanol resulted in a more extensively conjugated isomeric pyrido[1,2-*a*]quinazoline derivative (**178**), probably formed through a [1,5]-sigmatropic shift.⁶⁴



When the 6-ethoxy pyrido[1,2-*a*]quinazolines **137** ($R = R^1 = H$), **138** ($R = R^1 = H$), and **178** were heated in methanol in the presence of perchloric acid, the pyrido[1,2-*a*]quinazolin-6-ones **179** and **180** were obtained.⁶⁴

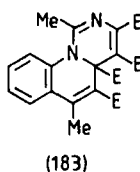
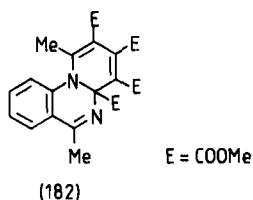
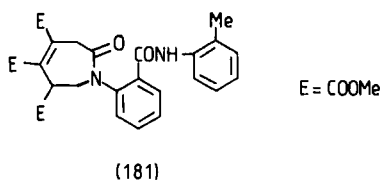
The azepino[1,2-*a*]quinazoline **140** was refluxed in formic acid to give the azepine **181** in 90% yield.⁶⁷

For further reactions of pyrido- and azepino[1,2-*a*]quinazolines, see also Section IV,A,1.

C. PHYSICOCHEMICAL PROPERTIES

For the pyrrolo[1,2-*a*]quinazolines, UV,^{29,40,47,48,50,60,71} IR,^{29,36,37,42,43,47,48,52,54,56,59,60,68,80} ¹H-NMR,^{30,33,36,37,40-43,47,48,50,52,54,68,71,80} ¹³C-NMR,⁵² and mass spectral⁵⁴ data are available; for the pyrido[1,2-*a*]quinazolines, UV,^{29,64,65,74,76,77} IR,^{29,43,56,74,76,78} ¹H-NMR,^{43,64,66,76,78} and ¹³C-NMR⁶⁴⁻⁶⁶ data are available; and for the azepino[1,2-*a*]quinazolines, UV,⁶⁷ IR,^{55,56,67} and ¹H-NMR^{55,67} data are available.

Some authors^{37,40,43,57} provide comparative data on the physicochemical properties of the isomeric linear and angular pyrrolo- and pyridoquinazo-



lines. The angularly fused pyrrolo- and pyrido[1,2-*a*]quinazolinones (**98**) in general have higher melting points and R_f values than the linear isomers **99**.^{40,43}

In view of the results of NMR studies on pyrido[1,2-*a*]quinazolines with lanthanide shift reagents, Acheson and co-workers⁶⁴ suggested that the adduct obtained from 2,4-dimethylquinazoline and dimethyl acetylenedicarboxylate is more likely to have structure **182** than the earlier proposed structure **183**.¹¹

D. APPLICATIONS

The following biological effects are mentioned in patents: for pyrrolo[1,2-*a*]quinazolines, CNS activity, including depressant,^{38,70,79} analgesic,²⁸ antipyretic,²⁸ and/or hypnotic⁵³ effects, as well as antiinflammatory,²⁸ anticonvulsive,⁵² antiedemic,^{28,29} mydriatic,⁷⁰ bronchodilator,⁸² antihypertensive,^{27,72} blood platelet aggregation inhibitory,⁷² and pesticide⁵² effects; for pyrido[1,2-*a*]quinazolines, analgesic,²⁸ antipyretic,²⁸ antiinflammatory,²⁸ bronchodilator,⁸² antihypertensive,^{27,72,79} and blood platelet aggregation inhibitory⁷² activities; and for azepino[1,2-*a*]quinazolines, antihypertensive⁷² and blood platelet aggregation inhibitory⁷² properties.

V. Other Linearly Annelated Ring Systems (Type III)

A. NATURALLY OCCURRING DERIVATIVES

Known pyrrolo[2,1-*b*]quinazoline and pyrido[2,1-*b*]quinazolinone alkaloids are named and depicted in Table II.

In 1888, Hooper⁸³ first investigated the pharmacological action of an extract of *Adhatoda vasica* Nees containing compound **184**. In 1925, Ghose and Sen isolated⁸⁴ this component and named it vasicine. In 1934, Späth and Nikawitz isolated⁸⁵ an alkaloid from *Peganum harmala* and named it peganine, but soon afterward Späth and Kuffner⁸⁶ showed it to be identical with vasicine. This alkaloid (**184**) was found not only in *Adhatoda*

⁸² W. J. Houlihan, German Patent 2,162,590 [CA 77, 118199 (1972)].

⁸³ D. Hooper, *Pharm. J.* [3] **18**, 841 (1888).

⁸⁴ S. N. Sen and T. P. Ghose, *J. Indian Chem. Soc.* **1**, 315 (1925).

⁸⁵ E. Späth and E. Nikawitz, *Chem. Ber.* **67**, 45 (1934).

⁸⁶ E. Späth and F. Kuffner, *Chem. Ber.* **67**, 868 (1934).

TABLE II
NATURALLY OCCURRING PYRROLO[2,1-*b*]QUINAZOLINES AND PYRIDO[2,1-*b*]QUINAZOLINES

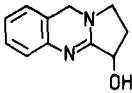
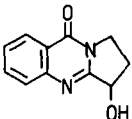
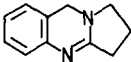
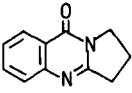
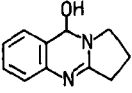
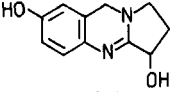
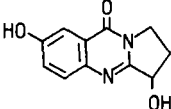
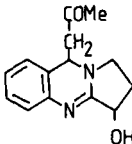
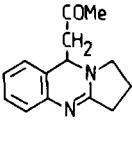
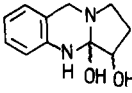
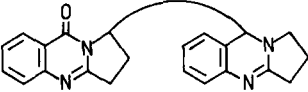
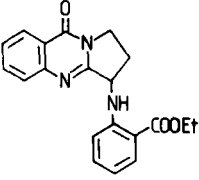
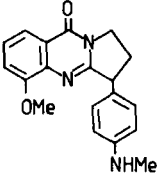
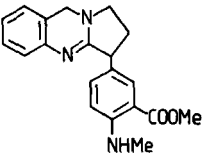
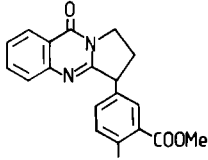
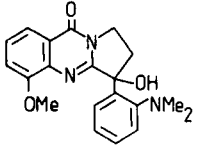
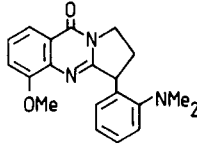
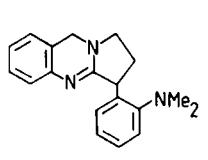
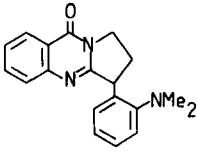
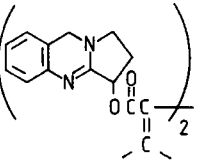
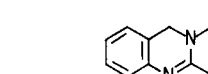

		
(184) vasicine peganine	(185) vasicinone oxopeganine	(124) deoxypeganine deoxyvasicine
		
(95) deoxyvasicinone oxodeoxypeganine	(186) peganol	(187) vasicinal
		
(188) vasicinolone	(189) peganidine	(190) deoxypeganidine
		
(191) vasicol	(192) dipepine	
		
(193) anisessine	(194) sessiflorine	(195) adhatodine

TABLE II (Continued)

 <p>(196) anisotine</p>	 <p>(197) aniflorine</p>	 <p>(198) deoxyaniflorine</p>
 <p>(199) vasicoline</p>	 <p>(200) vasicolinone</p>	 <p>(201) nordine</p>
 <p>(202)</p>	 <p>(203)</p>	

*vasica*⁸⁷⁻⁹⁹ and *Peganum harmala*,¹⁰⁰⁻¹²² but also in *Peganum nigellastrum*,^{119,123} *Anisotes sessiliflorus*,¹²⁴ and various *Linaria*,¹²⁵⁻¹²⁹ *Galega*,¹³⁰⁻¹³⁵ and *Side*¹³⁶⁻¹³⁸ species. Vasicine (184) has often been obtained as a racemic compound.^{105,123,124,130} However, in plants vasicine is probably present in the optically active form but racemizes during the process of isolation.¹³⁹ This was indicated¹⁴⁰ by the isolation of (-)-vasicine from *Peganum harmala* under special conditions. It is interesting to note that (+)-vasicine was isolated from *Galega officinalis*.¹³¹ Späth and Keszler¹⁴⁰ resolved racemic vasicine into its optically active antipodes by use of *d*-tartaric acid in methanol.

⁸⁷ T. P. Ghose, S. Krishna, K. S. Narang, and J. N. Ray, *J. Chem. Soc.*, 2740 (1932).

⁸⁸ A. K. De and J. N. Ray, *J. Indian Chem. Soc.* **4**, 541 (1927).

⁸⁹ I. B. M. Mithal and M. L. Schroff, *Indian Pharm.* **9**, 307 (1954).

⁹⁰ D. R. Mehta, Indian Patent 64,603 [*CA* **54**, 20096f (1960)].

⁹¹ D. R. Mehta, J. S. Naravane, and R. M. Desai, *J. Org. Chem.* **28**, 445 (1963).

⁹² M. Ikram, M. Ehsanul Huq, S. A. Warsi, and Vigar-Uddin Ahmad, *Pak. J. Sci. Ind. Res.* **8**, 76 (1965).

⁹³ M. Ikram and M. Ehsanul Huq, *Pak. J. Sci. Res.* **18**, 109 (1966).

The biogenesis and biosynthesis of vasicine (184) have been intensively studied.¹⁴¹⁻¹⁵⁴ Some comprehensive surveys have been made on its chemistry and pharmacology.¹⁵⁵⁻¹⁵⁹

Vasicinone (185) was found in *Adhatoda vasica*,^{92,95-99,107,122,160-162} *Peganum harmala*,^{105,106,110,111,114,119} *Peganum nigellastrum*,^{119,123} *Nitrasia sibirica*,¹⁶³ *Galega officinalis*,¹³⁰ *Biebersteinia multiflora*,¹¹⁵ *Linaria* species,^{127,164} and *Sida* species.¹³⁶⁻¹³⁸ Since the methylene group in the pyrimidine ring of vasicine (184) is easily oxidized by atmospheric oxygen, it was suggested^{57,91,107} that vasicinone (185) is isolated as an artifact. The glycosides and *N*-oxides of vasicine (184) and vasicinone (185) were detected in extracts from *Adhatoda vasica*.⁹⁹

Deoxypeganine or deoxyvasicine (124) was isolated from *Adhatoda vasica*,⁹⁹ *Peganum harmala*,^{109,111,115,119,165} and *Peganum nigellastrum*,¹¹⁹; deoxyvasicinone (95) from *Peganum harmala*,^{110,111,114,115,119,121,166,167} *Peganum nigellastrum*,^{119,123} *Adhatoda vasica*,^{95,168} *Linaria transiliensis*, and *Mackinlaya macrosciadia*,¹⁶⁹; peganol (186) from *Peganum harmala*,¹⁷⁰; and vasicinol (187) from *Adhatoda vasica*,^{98,171,172} and *Sida* species.^{136,138}

Vasicinolone (188) and adhatodine (195) were obtained from *Adhatoda vasica*,^{95,98} and anisotine (196) from *Adhatoda vasica*⁹⁵ and *Anisotes sessiliflorus*.¹²⁴

⁹⁴ M. Ehsanul Huq, M. Ikram, and S. A. Warsi, *Pak. J. Sci. Ind. Res.* **10**, 224 (1967).

⁹⁵ S. John, D. Gröger, and M. Hesse, *Helv. Chim. Acta* **54**, 826 (1971).

⁹⁶ J. L. D'Cruz, A. Y. Nimbkar, and C. K. Kokate, *Indian Drugs* **17**, 99 (1980).

⁹⁷ H. L. Balla, J. L. D'Cruz, and C. K. Kokate, *Indian Drugs* **20**, 16 (1982).

⁹⁸ M. P. Jain and V. K. Sharma, *Planta Med.* **46**, 250 (1982).

⁹⁹ K. Pandita, M. S. Bhatia, R. K. Thappa, S. G. Agarwal, K. L. Dhar, and C. K. Atal, *Planta Med.* **48**, 81 (1983).

¹⁰⁰ A. Rosenfel'd and D. G. Kolesnikow, *Chem. Ber.* **69**, 2022 (1936).

¹⁰¹ E. Späth and E. Zajic, *Chem. Ber.* **69**, 2448 (1936).

¹⁰² A. Rozenfel'd and D. G. Kolesnikow, *Trans. Ukr. Inst. Exp. Pharm.* **1**, 28 (1938) [*CA* **33**, 9306^b (1939)].

¹⁰³ A. F. Ovejero, *Farmacoter. Actual* **3**, 842 (1946) [*CA* **41**, 3214i (1946)].

¹⁰⁴ A. F. Ovejero, *Farmacognosia* **6**, 103 (1947).

¹⁰⁵ N. I. Koretskaya, *Zh. Obshch. Khim.* **27**, 3361 (1957) [*CA* **52**, 9163d (1958)].

¹⁰⁶ N. I. Koretskaya and L. M. Utkin, *Zh. Obshch. Khim.* **28**, 1087 (1958) [*CA* **52**, 18501c (1958)].

¹⁰⁷ A. H. Amin and D. H. Mehta, *Nature (London)* **184**, Suppl. (17), 1317 (1959).

¹⁰⁸ A. Schipper and O. H. Volk, *Dsch. Apoth.-Ztg.* **100**, 255 (1960) [*CA* **55**, 16913c (1961)].

¹⁰⁹ S. Siddiqui, *Pak. J. Sci. Ind. Res.* **5**, 207 (1962).

¹¹⁰ N. V. Plekhanova and S. T. Aktanova, *Issled. Flory Kirg. Alkaloidonosnost, Akad. Nauk Kirg. SSR, Inst. Org. Khim.*, 57 (1965) [*CA* **64**, 11550f (1966)].

¹¹¹ Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yusunov, *Khim. Priir. Soedin.*, 456 (1969) [*CA* **72**, 75670 (1970)].

Other compounds isolated from *Peganum harmala* included deoxypeganidine (190),^{118,173} peganidine (189),¹⁷³ and dipegine (192)¹⁷⁴; and from *Adhatoda vasica*, vasicoline (199),⁹⁵ vasicolinone (200),⁹⁵ and vasicol (191),^{98,162}

From *Anisotes sessiliflorine*, anisessine (193), aniflorine (197), deoxyaniflorine (198), and sessiliflorine (194) were obtained.¹²⁴ The proposed structure of sessiliflorine (194) was corrected by Onaka.¹⁷⁵

The bark of the "Sangre de Drage" tree contains a water-soluble red pigment called nordine (201).¹⁷⁶

From *Mackinlaya subulata* and *M. macrosciadia* the tetrahydropyr-ido[2,1-*b*]quinazoline 202 and its 11-oxo derivative 203 were obtained.^{170,177,178}

¹¹² L. K. Safine, R. G. Medvedeva, and L. D. Bryzgalova, *Tr. Inst. Bot., Akad. Nauk Kaz. SSR* **28**, 226 (1970) [CA 73, 127850 (1970)].

¹¹³ Kh. N. Khashimov, M. V. Telezhenetskaya, N. N. Sharakhimov, and S. Yu Yunusov, *Khim. Prir. Soedin.*, 382 (1971) [CA 75, 115865 (1971)].

¹¹⁴ A. I. Botbaev, N. V. Plekhanova, and E. V. Nikitina, *Izv. Akad. Nauk Kirg. SSR*, 52 (1974) [CA 81, 132770 (1974)].

¹¹⁵ D. Kurbanov and B. Kh. Zharekeev, *Khim. Prir. Soedin.*, 685 (1974) [CA 82, 83023 (1975)].

¹¹⁶ B. K. Mirzakhmedov, Kh. N. Aripov, T. T. Shakirov, M. V. Telezhenetskaya, N. N. Sharakhimov, and S. Yu. Yunusov, U.S.S.R. Patent 460,056 [CA 83, 84850 (1975)].

¹¹⁷ B. K. Mirzakhmedov, Kh. N. Aripov, and T. T. Shakirov, *Khim. Prir. Soedin.*, 432 (1975) [CA 84, 40725 (1976)].

¹¹⁸ S. H. Hilal, M. Y. Haggag, and S. A. El-Kashoury, *Egypt. J. Pharm. Sci.* **18**, 9 (1977) [CA 92, 18856 (1980)].

¹¹⁹ D. Batsuren, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 736 (1980) [CA 94, 99791 (1981)].

¹²⁰ S. H. Hilal, M. Y. Haggag, F. M. Soliman, and S. El-Kashoury, *Egypt. J. Pharm. Sci.* **19**, 393 (1978) [CA 94, 188683 (1981)].

¹²¹ A. Al-Shamma, S. Drake, D. L. Flynn, L. A. Mitscher, Y. H. Park, G. S. R. Rao, A. Simpson, J. K. Swayze, T. Veysoglu, and S. T. S. Wu, *J. Nat. Prod.* **44**, 745 (1981).

¹²² K. R. Brain and B. B. Thaga, *J. Chromatogr.* **258**, 183 (1983).

¹²³ D. Batsuren, M. V. Telezhenetskaya, S. Yu. Yunusov, and T. Baldan, *Khim. Prir. Soedin.*, 418 (1978) [CA 89, 126170 (1978)].

¹²⁴ R. R. Arndt, S. H. Eggers, and A. Jordaan, *Tetrahedron* **23**, 3521 (1967).

¹²⁵ G. P. Men'shikov, A. I. Ban'kovskii, and V. I. Frolova, *Zh. Obshch. Khim.* **29**, 3846 (1959).

¹²⁶ D. Gröger and S. Johnne, *Planta Med.* **13**, 182 (1965).

¹²⁷ N. V. Plekhanova and G. P. Sheveleva, *Issled. Flory Kirg. Alkaloidonosnost, Akad. Nauk Kirg. SSR, Inst. Org. Khim.*, 54 (1965) [CA 64, 11550e (1966)].

¹²⁸ S. Johnne and D. Gröger, *Pharmazie* **23**, 35 (1968).

¹²⁹ M. Pinar, *An. Quim.* **71**, 834 (1975) [CA 84, 147706 (1976)].

¹³⁰ V. P. Linyuchev and A. I. Ban'kovskii, *Tr. Vses. Nauchno-Issled. Inst. Lek. Aromat. Rast.*, 65 (1959) [CA 55, 18893e (1961)].

¹³¹ K. Schreiber, O. Aurich, and K. Pufahl, *Arch. Pharm. (Weinheim, Ger.)* **295**, 271 (1962).

¹³² G. Reuter, *Planta Med.* **10**, 226 (1962).

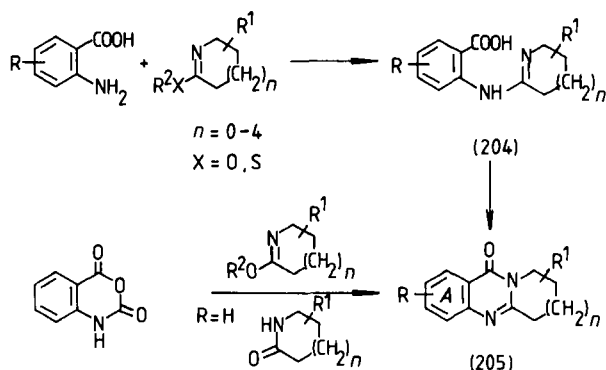
B. SYNTHESSES

1. From Anthranilic Acid and Its Derivatives

One of the most widely used synthetic methods for preparation of the linearly annelated tricycles **205**, containing a six-membered aromatic ring A, is the cyclocondensation of anthranilic acids and lactim ethers.^{175,179-188}

Cyclocondensations have been carried out without solvent¹⁸⁰ or in solutions in acetone,¹⁷⁹⁻¹⁸¹ alcohol,^{178,186,188} chloroform,¹⁸⁰ benzene,^{175,182,185,187} or ethylene glycol monomethyl ether acetate.^{183,184} Besides lactim ethers, lactim thioethers have been used as reaction partners of anthranilic acids.^{179,180}

Under mild conditions the condensation products **204** could be isolated, and they were cyclized by heating in acetic acid.^{179,180}



¹³³ J. Schaefer and M. Stein, *Naturwissenschaften* **54**, 205 (1967).

¹³⁴ E. Richter, *Theor. Appl. Genet.* **38**, 118 (1968).

¹³⁵ J. Schaefer and M. Stein, *Biol. Zentralbl.* **88**, 755 (1969).

¹³⁶ S. Ghosal, R. B. P. S. Chauhan, and R. Mehta, *Phytochemistry* **14**, 830 (1975).

¹³⁷ A. A. L. Gunatilaka, S. Sotheeswaran, S. Balasubramaniam, A. I. Chandrasekara, and H. T. B. Sriyani, *Planta Med.* **39**, 66 (1980).

¹³⁸ A. Prakash, R. K. Varma, and S. Ghosal, *Planta Med.* **43**, 384 (1981).

¹³⁹ E. Späth, F. Kuffner, and N. Platzer, *Chem. Ber.* **68**, 1384 (1935).

¹⁴⁰ E. Späth and F. Keszler, *Chem. Ber.* **69**, 384 (1936).

¹⁴¹ D. Gröger and K. Mothes, *Arch. Pharm. (Weinheim, Ger.)* **293**, 1049 (1960).

¹⁴² D. Gröger, S. John, and K. Mothes, *Experientia* **21**, 13 (1965).

¹⁴³ D. Gröger and S. John, *Beitr. Biochem. Physiol. Naturst.*, 205 (1965) [*CA* **64**, 20215b (1966)].

¹⁴⁴ D. Gröger, S. John, and K. Mothes, *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.*, 581 (1966) [*CA* **66**, 102526 (1967)].

¹⁴⁵ D. Gröger, S. John, and K. Mothes, *Experientia* **23**, 812 (1967).

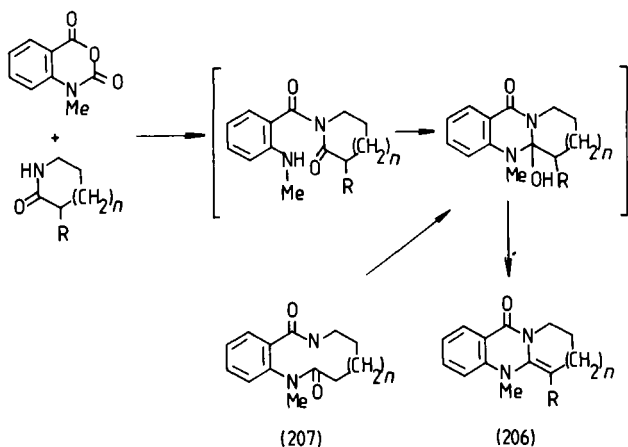
¹⁴⁶ S. John and D. Gröger, *Phytochemistry* **7**, 429 (1968).

3-Nitro- and 3,5-dinitroanthranilic acids failed to react.¹⁸³

Soviet researchers treated anthranilic acids and lactams with phosphoryl chloride to obtain the tricyclic compounds **205** in 25–80% yields.^{189–194} Ring closure probably takes place in the imidoyl chlorides formed *in situ* from the lactams.^{189–194}

Stephen and Stephen¹⁹⁵ set out from 2-chloro-3,4,5,6-tetrahydropyridine and methyl anthranilate and obtained the pyrido[2,1-*b*]quinazolinone **205** ($R = R^1 = H, n = 1$) in 75% yield. Alkyl anthranilates were also treated with lactim ethers¹⁹⁶ and lactams.¹⁹⁷

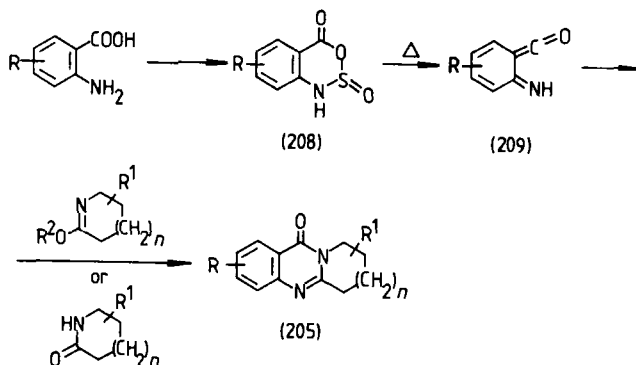
Tricyclic compounds of type **205** were produced in about 50% yield from the reactions of isatoic anhydride with lactams^{198–200} and lactim ethers.^{179,180} When *N*-methylisatoic anhydride was applied instead of isatoic anhydride, the products were the unstable enamines **206**, which may undergo further transformations depending on the reaction conditions.^{181,201,202}



- ¹⁴⁷ D. R. Libjegen, *Phytochemistry* **7**, 1299 (1968).
¹⁴⁸ S. Johne, D. Gröger, and G. Richter, *Arch. Pharm. (Weinheim, Ger.)* **301**, 721 (1968).
¹⁴⁹ L. Skursky and L. Macholan, *Acta Fac. Rerum Nat. Univ. Comenianae, Chim.*, 335 (1968) [CA **71**, 27857 (1969)].
¹⁵⁰ S. Johne and D. Gröger, *Z. Pflanzenphysiol.* **61**, 353 (1969).
¹⁵¹ D. R. Liljegen, *Phytochemistry* **10**, 2661 (1971).
¹⁵² K. Waiblinger, S. Johne, and D. Gröger, *Phytochemistry* **11**, 2263 (1972).
¹⁵³ K. A. Zirvi and A. Butt, *Pak. J. Sci. Ind. Res.* **14**, 344 (1971).
¹⁵⁴ S. Johne, K. Waiblinger, and D. Gröger, *Pharmazie* **28**, 403 (1973).
¹⁵⁵ A. P. Orekhov, *Bull. Acad. Sci. U.R.S.S., Cl. Sci. Math. Nat., Ser. Chim.*, 935 (1936) [CA **31**, 5365³ (1937)].
¹⁵⁶ E. Späth, *Monatsh. Chem.* **72**, 115 (1938).
¹⁵⁷ J. N. Rây, *J. Indian Chem. Soc.* **35**, 697 (1958).
¹⁵⁸ I. M. Sharapov, *Farmakol. Toksikol. (Moscow)* **22**, 69 (1959) [CA **53**, 20578i (1959)].

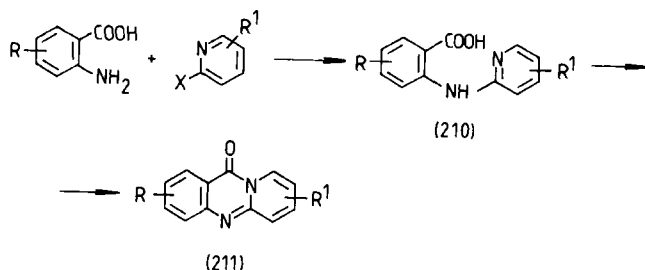
Compounds **206** were also formed as the dehydration products of the cyclodipeptides **207**.^{201,203}

Kametani *et al.*^{204–207} developed a facile synthesis of the tricyclic compounds **205** through the cycloaddition of lactim ethers^{204–206} and lactams^{204,206–210} with the iminoketene **209**, generated *in situ* from anthranilic acid and thionyl chloride via the sulfinamide anhydride **208**. The yield was higher when the lactam was used in the reaction.²⁰⁶



From anthranilic acids and 2-halopyridines, the unsaturated 11*H*-pyrido[2,1-*b*]quinazolin-11-ones **211** were prepared.^{200,211–237}

- ¹⁵⁹ C. K. Atal, in "Chemistry and Pharmacology of Vasicine: A New Oxytocic and Abortifacient" (C. K. Atal, ed.), p. 155. Regional Research Laboratory, Jammu-Tawi, India, 1980.
- ¹⁶⁰ M. K. Choudhury, *Naturwissenschaften* **66**, 205 (1979).
- ¹⁶¹ M. K. Choudhury and P. Chakrabarti, *Indian Agric.* **21**, 225 (1977).
- ¹⁶² K. L. Dhar, M. P. Jain, S. K. Koul, and C. K. Atal, *Phytochemistry* **20**, 319 (1981).
- ¹⁶³ Z. Osmanov, A. A. Ibragimov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 126 (1982) [CA **97**, 20680 (1982)].
- ¹⁶⁴ D. Gröger and S. John, *Pharmazie* **20**, 456 (1965).
- ¹⁶⁵ E. K. Dobronravova and T. T. Shakirov, *Khim. Prir. Soedin.*, 677 (1976) [CA **86**, 85573 (1977)].
- ¹⁶⁶ Kh. N. Aripov, B. K. Mirzakhmedov, T. T. Shakirov, E. D. Dobronravova, M. V. Telezhenskaya, S. Yu. Yunusov, and T. U. Rakhmatullaev, U.S.S.R. Patent 878,295 [CA **96**, 91639 (1982)].
- ¹⁶⁷ A. Chatterjee and M. Ganguly, *Phytochemistry* **7**, 307 (1968).
- ¹⁶⁸ M. P. Jain, S. K. Koul, K. L. Dhar, and C. K. Atal, *Phytochemistry* **19**, 1880 (1980).
- ¹⁶⁹ N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.* **24**, 223 (1971).
- ¹⁷⁰ M. V. Telezhenskaya, Kh. N. Kashimov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 849 (1971) [CA **76**, 110310 (1972)].
- ¹⁷¹ F. Kuffner, G. Lenneis, and H. Bauer, *Monatsh. Chem.* **91**, 1152 (1960).
- ¹⁷² A. K. Bhatnagar, S. Bhattacharji, and S. P. Popli, *Indian J. Chem.* **3**, 524 (1965).
- ¹⁷³ B. Kh. Zharekeev, M. V. Telezhenskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 279 (1973) [CA **79**, 32158 (1973)].



Cyclocondensations were carried out by heating in the melt^{200,211-217,232}, in the presence of potassium iodide^{218-221,229}, in triglyme^{224,235}; in acetic acid^{222,223}; in ethanol containing concentrated hydrochloric acid^{219,223,225-227,233,234,237}; in ethylene glycol monomethyl ether containing formic acid²²⁴; in the presence of *N*-ethylmorpholine, potassium carbonate, and cupric bromide in ethylene glycol monobutyl ether or diethylene glycol dimethyl ether^{230,231}; in the presence of copper bronze and potassium carbonate^{228,229}; and in the presence of 18-crown-6.²³⁶

Alkyl anthranilates^{232,237-240} and 2-halopyridine *N*-oxides²³⁸ were also used as starting materials.

¹⁷⁴ B. Kh. Zharekeev, Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 264 (1974) [CA 81, 13681 (1974)].

¹⁷⁵ T. Onaka, *Tetrahedron Lett.*, 4387 (1971).

¹⁷⁶ E. Sodi Pallares, *Arch. Biochem.* 10, 235 (1946) [CA 40, 6487¹ (1946)].

¹⁷⁷ S. R. Johns and J. A. Lamberton, *Chem. Commun.*, 267 (1965).

¹⁷⁸ J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. H. Redcliffe, *Aust. J. Chem.* 19, 151 (1966).

¹⁷⁹ S. Petersen and E. Tietze, *Justus Liebigs Ann. Chem.* 623, 166 (1959).

¹⁸⁰ S. Petersen and E. Tietze, German Patent 1,088,968 [CA 55, 27381b (1961)].

¹⁸¹ A. M. Shkrob, Yu. I. Krylova, V. K. Antonov, and M. M. Shemyakin, *Zh. Obshch. Khim.* 38, 2030 (1968) [CA 70, 47397 (1969)].

¹⁸² G. Devi, R. S. Kapil, and S. P. Popli, *Indian J. Chem., Sect. B* 14B, 354 (1976).

¹⁸³ S. Johne, B. Jung, D. Gröger, and R. Radeglia, *J. Prakt. Chem.* 319, 919 (1977).

¹⁸⁴ C. Bergner, D. Gröger, J. Siegfried, B. Jung, K. Schreiber, and G. Sembdner, German (East) Patent 128,758 [CA 89, 101913 (1978)].

¹⁸⁵ N. Mohr, H. Budzikiewicz, H. Korth, and G. Pulverev, *Justus Liebigs Ann. Chem.*, 1515 (1981).

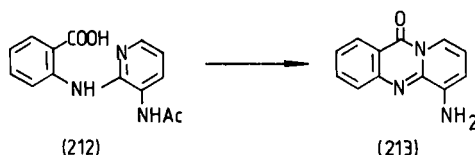
¹⁸⁶ M. Langlios, C. Guilloneau, TriVo Van, R. Jolly, and J. Maillard, *J. Heterocycl. Chem.* 20, 393 (1983).

¹⁸⁷ I. Hermecz, B. Podányi, Z. Mészáros, J. Kökösi, Gy. Szász, and G. Tóth, *J. Heterocycl. Chem.* 20, 93 (1983).

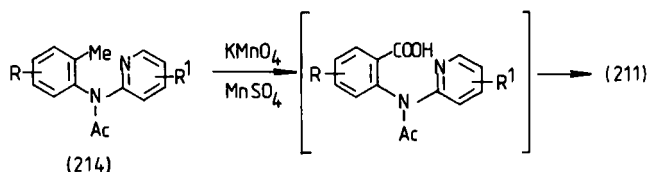
¹⁸⁸ R. G. Glushkov and O. Yu. Magidson, *Zh. Obshch. Khim.* 31, 189 (1961) [CA 55, 22336c (1961)].

¹⁸⁹ Kh. M. Shakhidoyatov, A. Irisbaev, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 681 (1974) [CA 82, 86470 (1975)].

Italian authors succeeded in isolating the condensation product **210** ($R = H$, $R^1 = H$, $NHAc$), which cyclized upon heating above its melting point or by the action of acid (concd H_2SO_4 or concd HCl).^{216,241,242} Cyclization of the acetamide **212** was accompanied by hydrolysis of the acetamido group.²⁴²

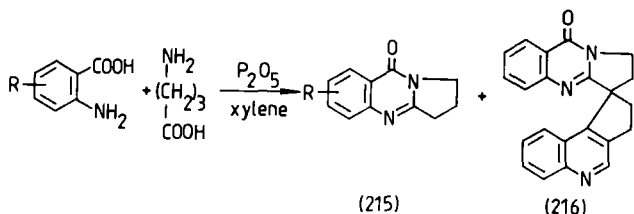


Schromm *et al.*²¹⁷ obtained the pyrido[2,1-*b*]quinazolines **211** by the oxidation of the pyridine derivatives **214** with potassium permanganate at 40–90°C in the presence of magnesium sulfate.

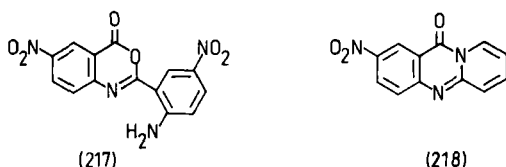


- ¹⁹⁰ A. Irisbaev, Kh. M. Shakhidoyatov, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 435 (1975) [*CA* **84**, 105879 (1976)].
- ¹⁹¹ Kh. M. Shakhidoyatov, A. Irisbaev, L. M. Yun, E. Oripov, and Ch. Sh. Kadyrov, *Khim. Geterotsikl. Soedin.*, 1564 (1976) [*CA* **86**, 106517 (1977)].
- ¹⁹² Kh. M. Shakhidoyatov and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 544 (1977) [*CA* **88**, 6830 (1978)].
- ¹⁹³ A. Karimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 498 (1982) [*CA* **98**, 72516 (1983)].
- ¹⁹⁴ A. Karimov, V. N. Plugar, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 396 (1983) [*CA* **99**, 122735 (1983)].
- ¹⁹⁵ T. Stephen and H. Stephen, *J. Chem. Soc.*, 4694 (1956).
- ¹⁹⁶ T. Nagasaka, F. Hamaguchi, N. Ozawa, and S. Ohki, *Heterocycles* **9**, 1375 (1978).
- ¹⁹⁷ G. G. Muñoz and R. Madroñero, *Chem. Ber.* **95**, 2182 (1962).
- ¹⁹⁸ E. Späth and N. Platzer, *Chem. Ber.* **68**, 2221 (1935).
- ¹⁹⁹ O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc. C*, 1722 (1968).
- ²⁰⁰ E. Späth and F. Kuffner, *Chem. Ber.* **71**, 1657 (1938).
- ²⁰¹ A. M. Shkrob, Yu. I. Krylova, V. K. Antonov, and M. M. Shemyakin, *Tetrahedron Lett.*, 2701 (1967).
- ²⁰² A. M. Shkrob, Yu. I. Krylova, V. K. Antonov, and M. M. Shemyakin, *Zh. Obshch. Khim.* **38**, 2051 (1968) [*CA* **70**, 77902 (1969)].
- ²⁰³ Yu. I. Krylova, A. M. Shkrob, V. K. Antonov, and M. M. Shemyakin, *Zh. Obshch. Khim.* **38**, 2046 (1968) [*CA* **70**, 20034 (1969)].
- ²⁰⁴ T. Kametani, Chu Van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *Heterocycles* **4**, 1487 (1976).

The pyrrolo[2,1-*b*]quinazolines **215** were synthesized by mixing anthranilic acids and γ -aminobutyric acid in the presence of phosphorus pentoxide in refluxing xylene.^{167,183} With anthranilic acid as starting compound, the spiro product **216** was also isolated from the reaction mixture.¹⁶⁷

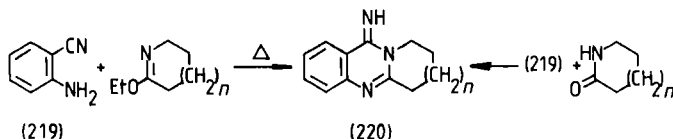


5-Nitroanthranilic acid reacted with *p*-toluenesulfonyl chloride in pyridine to give the benzoxazine **217** and the 2-nitropyrido[2,1-*b*]quinazoline **218** in 26 and 72% yields, respectively, at room temperature, and in 59 and 29% yields, respectively, at 114°C.^{243,244}



- ²⁰⁵ T. Kametani, T. Higa, Chu Van Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Am. Chem. Soc.* **98**, 6186 (1976).
- ²⁰⁶ T. Kametani, Chu Van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *J. Am. Chem. Soc.* **99**, 2306 (1977).
- ²⁰⁷ T. Kametani, K. Fukumoto, M. Ihara, and Chu Van Loc, *Symp. Heterocycl., [Pap.]*, 243 (1977) [*CA* **89**, 163805 (1978)].
- ²⁰⁸ M. Koizumi, I. Matsuura, and Y. Murakami, Japan Kokai 77/77,093 [*CA*, **88**, 6930 (1978)].
- ²⁰⁹ T. Kametani, Japan Kokai 78/77,075 [*CA* **89**, 180037 (1978)].
- ²¹⁰ Farmitalia Carlo Erba S.p.A., Netherlands Patent Appl. 82/02,602 [*CA* **99**, 38481 (1983)].
- ²¹¹ A. Reissert, *Chem. Ber.* **28**, 119 (1895).
- ²¹² P. K. Bose and D. C. Len, *J. Chem. Soc.*, 2840 (1931).
- ²¹³ A. Binz and C. Räth, *Justus Liebigs Ann. Chem.* **486**, 284 (1931).
- ²¹⁴ O. A. Seide and G. V. Tschelinzew, *J. Gen. Chem. USSR (Engl. Transl.)* **7**, 2314 (1937) [*CA* **32**, 572¹ (1938)].
- ²¹⁵ C. Räth, German Patent 522,272; Fridlaender, **17**, 2561 (1932).
- ²¹⁶ S. Carboni and D. Segnini, *Gazz. Chim. Ital.* **85**, 1210 (1955).
- ²¹⁷ K. Schromm, A. Mentrup, E. O. Repth, and A. Fuegner, German Patent 2,557,425 [*CA* **87**, 117898 (1977)]; U.S. Patent 4,332,802 [*CA* **97**, 144870 (1982)].
- ²¹⁸ Laboratorives U.P.S.A., Netherlands Patent Appl. 6,414,717 [*CA* **64**, 712h (1966)].
- ²¹⁹ C. F. Schwender and B. R. Sunday, German Patent 2,645,110 [*CA* **87**, 23327 (1976)].
- ²²⁰ J. W. Tilley, R. A. LeMahieu, M. Carson, R. W. Kierstead, H. W. Baruth, and B. Yaremko, *J. Med. Chem.* **23**, 92 (1980).

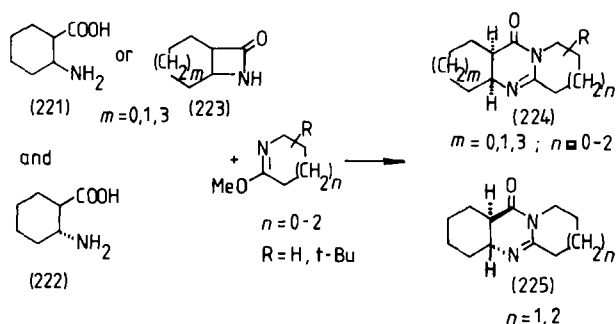
Brown and Ienage²⁴⁵ obtained the tricyclic imines **220** by treating anthranilonitrile **219** with lactim ethers ($n = 2-4$) at 150–190°C for 24–36 hr. The tricyclic imines **220** were also synthesized through the cyclodehydration of anthranilonitrile (**219**) with lactams ($n = 2-4, 6$) by the use of phosphorus pentoxide in boiling xylene.



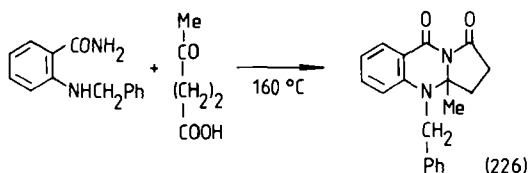
The reactions of *cis*- and *trans*-hexahydroanthranilic acids (**221** and **222**) with lactim ethers in boiling inert solvents gave the *cis* and *trans* tricyclic compounds **224** and **225**.^{180,246–249} The yield was poor if the reaction was carried out in benzene in the presence of phosphoryl chloride.²⁴⁸

The *cis* derivatives **224** were also obtained in the reaction of the bicyclic azetidinones **223** and lactim ethers.^{247,248,250,251}

- ²²¹ R. W. Kierstead and J. W. Tilley, German Patent 2,812,585 [CA 90, 87500 (1979)].
- ²²² V. A. Petrow, *J. Chem. Soc.*, 927 (1945).
- ²²³ C. F. Schwender, B. R. Sunday, B. J. Herzig, E. K. Kusner, P. R. Schumann, and D. L. Gawlak, *J. Med. Chem.* **22**, 748 (1979).
- ²²⁴ J. W. Tilley, P. Levitan, A. F. Welton, and H. J. Crowley, *J. Med. Chem.* **26**, 1638 (1983).
- ²²⁵ C. F. Schwender and B. R. Sunday, U.S. Patent 4,066,767 [CA 88, 136658 (1978)].
- ²²⁶ C. F. Schwender and B. R. Sunday, South African Patent 78/04,057 [CA 92, 111050 (1980)].
- ²²⁷ C. F. Schwender, B. R. Sunday, and V. L. Decker, *J. Med. Chem.* **25**, 742 (1982).
- ²²⁸ T. Kappe and W. Lube, *Chem. Ber.* **112**, 3424 (1979).
- ²²⁹ R. Wintersteiger and O. S. Wolfbeis, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **38B**, 248 (1983).
- ²³⁰ H. Biere and J. F. Kapp, German Patent 2,739,020 [CA 90, 204131 (1979)].
- ²³¹ H. Biere, J. F. Kapp, and I. Boettcher, German Patent 2,845,766 [CA 93, 186397 (1980)].
- ²³² R. Altiparmakian, *Helv. Chim. Acta* **61**, 1146 (1978).
- ²³³ M. I. Fernandez Fernandez, C. Fuentes Manso, M. Izquierdo Sanjose, and M. L. Lucero de Pablo, Spanish Patent 511,866 [CA 100, 68317 (1984)].
- ²³⁴ M. I. Fernandez Fernandez, C. Fuentes Manso, M. Izquierdo Sanjose, and M. L. Lucero de Paslo, Spanish Patent 511,163 [CA 100, 139136 (1984)].
- ²³⁵ W. J. Tilley, European Patent Appl. 94,080 [CA 100, 174846 (1984)].
- ²³⁶ M. Izquierdo Sanjose, M. I. Fernandez Fernandez, and C. Fuentes Manso, Spanish Patent 499,375 [CA 97, 55830d (1982)].
- ²³⁷ M. I. Fernandez Fernandez, C. Fuentes Manso, M. Izquierdo Sanjose, A. Mosqueira Toribio, and M. L. Lucero de Pablo, Spanish Patent 513,504 [CA 103, 123510 (1985)].
- ²³⁸ R. W. Kierstead and J. W. Tilley, German Patent 2,812,586 [CA 90, 38953 (1979)].
- ²³⁹ C. F. Schwender, B. R. Sunday, and D. J. Herzig, *J. Med. Chem.* **22**, 114 (1979).
- ²⁴⁰ T. M. Paterson, R. K. Smalley, H. Suschitzky, and A. J. Barker *J. C. S. Perkin I*, 633 (1980).
- ²⁴¹ S. Carboni, *Atti Soc. Toscana Sci. Nat. Pisa, Mem., Ser. A* **62**, 261 (1955) [CA 50, 16767 (1956)].



The reaction of 2-(benzylamino)benzamide and 4-oxopentanoic acid at 160°C gave the hexahydropyrrolo[2,1-*b*]quinazoline-1,9-dione **226**.³⁶



De Martino *et al.*^{252,253} prepared the pyrrolo[2,1-*b*]quinazolones **231** starting from 2-nitrobenzoyl chlorides and diethyl aminomalonate. Treatment of the 2-nitrobenzoylaminomalonates **227** with acrolein and crotonaldehyde in the presence of sodium ethoxide gave the 5-hydroxy-1-(2-nitrobenzoyl)pyrrolidine-2,2-dicarboxylates **228**, which furnished the cor-

²⁴² P. Corti, E. Lencioni, C. Aprea, L. Micheli, and C. Murrazn, *Boll. Chim. Farm.* **123**, 95 (1984).

²⁴³ M. V. Loseva, B. M. Bolotin, and Yu. S. Ryabokobylko, *Khim. Geterotsikl. Soedin.*, 1003 (1972) [CA **77**, 139958 (1972)].

²⁴⁴ M. V. Loseva and B. M. Bolotin, *Khim. Geterotsikl. Soedin.*, 1341 (1972) [CA **78**, 43392 (1973)].

²⁴⁵ D. J. Brown and K. Ienage, *J. C. S. Perkin I*, 2182 (1975).

²⁴⁶ I. Hermecz, F. Fülöp, Z. Mészáros, G. Bernáth, and J. Knoll, German Patent 2,836,449 [CA **91**, 57048 (1979)].

²⁴⁷ G. Bernáth, G. Tóth, F. Fülöp, Gy. Göndös, and L. Gera, *J. C. S. Perkin I*, 1765 (1979).

²⁴⁸ G. Bernáth, G. Tóth, F. Fülöp, Gy. Göndös, and L. Gera, *Magy. Kem. Foly.* **86**, 232 (1980) [CA **94**, 15667 (1981)].

²⁴⁹ F. Fülöp, I. Huber, G. Bernáth, G. Tóth, K. Simon, I. Hermecz, and Z. Mészáros, *Heterocycles* **21**, 678 (1984).

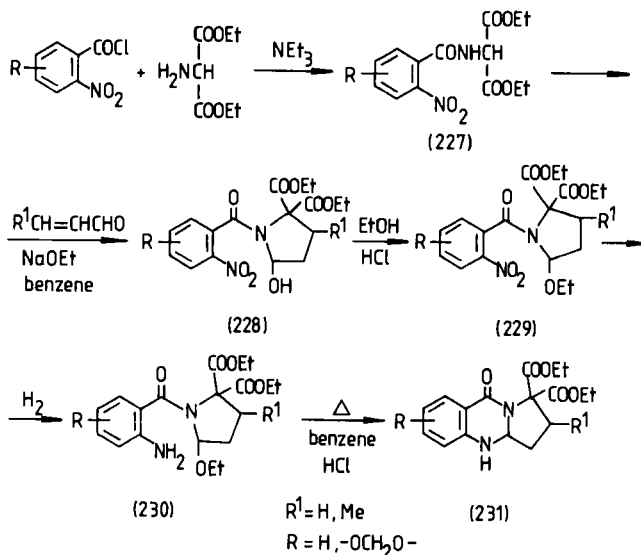
²⁵⁰ D. Bormann, *Chem. Ber.* **103**, 1797 (1970).

²⁵¹ D. Bormann, German Patent 1,803,785 [CA **73**, 35400 (1970)].

²⁵² G. De Martino, S. Massa, and G. Valitutti, *Farmaco, Ed. Sci.* **29**, 579 (1974).

²⁵³ S. Massa and G. De Martino, *Farmaco, Ed. Sci.* **33**, 271 (1978).

responding ethers **229** when treated with dry hydrogen chloride in ethanol. Catalytic reduction of the pyrrolidine-2,2-dicarboxylates **229** gave the corresponding amino derivatives **230**, which were transformed into the 9-oxo-hexanhydro[2,1-*b*]quinazoline-1,1-dicarboxylates **231** by heating in benzene in the presence of gaseous hydrogen chloride.



Cyclization of the 2-substituted quinazolinones **232**, **234**, and **236**, prepared from anthranilamides, afforded the pyrrolo[2,1-*b*]quinazolinones **233**, **235**, and **237**.²⁵⁴⁻²⁵⁸

The 2-substituted quinazolines **242** and **243** were obtained from *O*-ethylsuccinimide and the anilines **238** via the pyrrolo[2,1-*b*]quinazolines **240** and **241**.¹⁹⁶ The tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione **241** was isolated as a by-product from the reaction mixture of **243** and was also prepared from **239** (R = OMe) by heating at 142°C.

Further syntheses giving rise to mixtures of angularly and linearly annealed tricycles are discussed in Section IV,A,1 of this chapter.

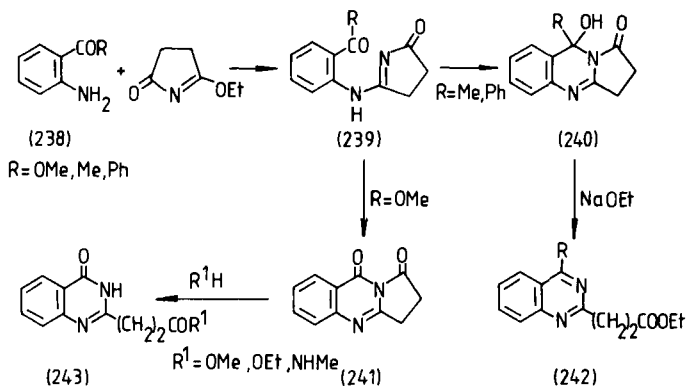
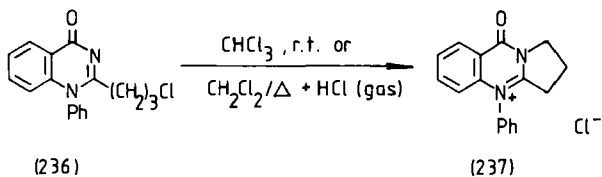
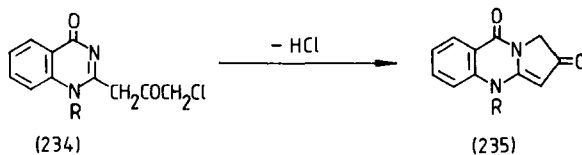
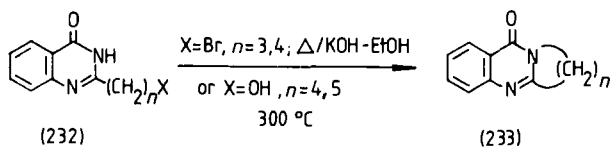
²⁵⁴ R. C. Morris, W. E. Hanford, and R. Adams, *J. Am. Chem. Soc.* **57**, 951 (1935).

²⁵⁵ K. Noda, A. Nakagawa, S. Yamazaki, K. Noguchi, T. Hachitani, and H. Ide, Japan Kokai 77/144,697 [*CA* **88**, 190879 (1978)].

²⁵⁶ K. Ozaki, Y. Yamada, and T. Oine, *Chem. Pharm. Bull.* **28**, 702 (1980).

²⁵⁷ H. Böhme and H. Böing, *Arch. Pharm. (Weinheim, Ger.)* **294**, 556 (1961).

²⁵⁸ H. Möhrle and Ch. M. Seidel, *Arch. Pharm. (Weinheim, Ger.)* **309**, 542 (1976).



2. From α -Amino Nitrogen Heterocycles

The pyrido[2,1-*b*]quinazolin-11-ones **211** were also prepared from 2-aminopyridines and 2-chlorobenzoic acid under similar conditions as applied in the reaction of anthranilic acids and 2-halopyridines.^{229-231,259,260}

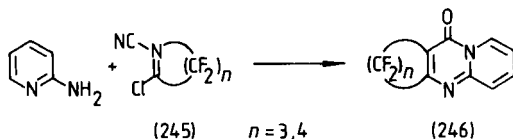
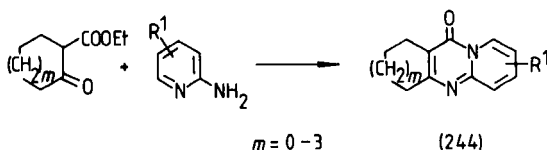
²⁵⁹ O. Seide, *Justus Liebigs Ann. Chem.* **440**, 311 (1924).

²⁶⁰ N. S. Zefirov, L. A. Aslanov, L. Rodes, N. M. Yur'eva, S. S. Trach, Yu. N. Luzikov, V. M. Jonov, and V. B. Rybakov, *Zh. Org. Khim.* **14**, 2407 (1978) [*CA* **90**, 137762 (1979)].

2-Aminopyridines were treated with cyclic β -oxo esters to give the tricyclic compounds **244**. Cyclocondensation was carried out in diethylbenzene,^{261,262} ethylene glycol monomethyl ether,^{262,263} acetic acid,^{232,240,263–265} polyphosphoric acid,^{217,246,266–268} ethyl polyphosphate,²⁶⁹ a mixture of phosphoryl chloride and polyphosphoric acid,^{246,266,267} or in the presence of *p*-toluenesulfonic acid^{262,263} in *N*-methyl-2-pyrrolidinone.²⁷⁰

The tricyclic compounds **244** were likewise obtained when 2-aminopyridinium halides were treated with β -oxo esters in boiling pyridine.^{246,266} Best yields were attained when 2-aminopyridinium iodides were applied.

Instead of β -oxo esters, their enamine derivatives^{265,270–272} and β -oxo carboxamides^{246,266} have also been used.



On heating in ethyl acetate, 2-aminopyridine and the fluorinated α -chloro nitriles **245** gave the fluorinated tricyclic compounds **246**.²⁷³

²⁶¹ H. L. Yale, U.S. Patent 3,965,100 [CA 85, 177477 (1976)].

²⁶² H. L. Yale, *J. Heterocycl. Chem.* **14**, 207 (1977).

²⁶³ A. M. P. Adrianus, German Patent 2,436,481 [CA 83, 35698 (1975)].

²⁶⁴ T. Yokoyama, K. Shibata, O. Fujii, and E. Iwamoto, Japan Kokai 76/43,799 [CA 85, 95806 (1976)].

²⁶⁵ Y. Yokoyama, K. Shibata, O. Fujii, and E. Iwamoto, *Toyo Soda Kenkyu Hokoku* **19**, 71 (1975) [CA 85, 125771 (1976)].

²⁶⁶ G. Bernáth, F. Fülöp, I. Hermecz, Z. Mészáros, and G. Tóth, *J. Heterocycl. Chem.* **16**, 137 (1979).

²⁶⁷ F. Fülöp, G. Bernáth, I. Hermecz, and Z. Mészáros, *Acta Phys. Chem.* **25**, 79 (1979).

²⁶⁸ G. Doria, C. Passarotti, P. P. Lovisolò, and A. Buttinoni, German Patent 3,315,299 [CA 100, 121098 (1984)].

²⁶⁹ T. H. Brown and K. Bowden, *J. Chem. Soc. C*, 2163 (1971).

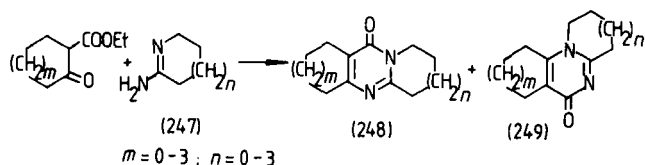
²⁷⁰ Y. Yokoyama, K. Shibata, O. Fujii, and E. Iwamoto, *Bull. Chem. Soc. Jpn.* **48**, 591 (1975).

²⁷¹ A. Halleux and H. G. Viehe, *J. Chem. Soc. C*, 881 (1971).

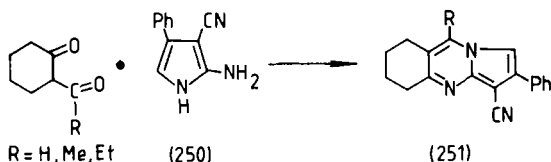
²⁷² T. Yokoyama, K. Shibata, O. Fujii, and E. Iwamoto, Japan Kikai 76/43,800 [CA 85, 178985 (1976)].

²⁷³ A. Ya. Il'chenko, V. I. Krokhtyak, and L. M. Yagupol'skii, *Khim. Geterotsikl. Soedin.*, 1407 (1982) [CA 98, 72044 (1983)].

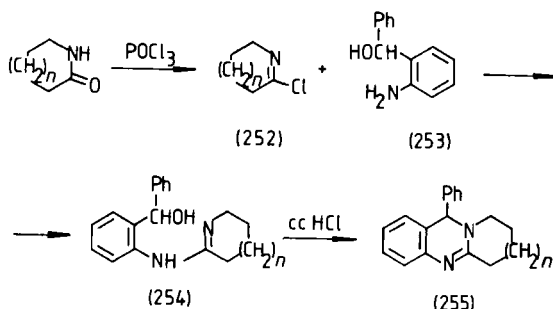
Reaction of the cyclic amidines **247** with cyclic β -oxo esters yielded both possible linear and angular tricyclic derivatives **248** and **249** but generally only the linearly annelated major products **248** were isolated.^{246,266,274-276} The yield of the angular isomer **249** decreased²⁷⁴ with increasing ring size.



The 2-amino-4-phenylpyrrole-3-nitrile **250** was condensed with 2-acylcyclohexanones in refluxing pyridine or acetic acid to yield the pyrrolo-[2,1-*b*]quinazolines **251**.²⁷⁷



The imidoyl chlorides **252** and the 2-aminobenzhydrol **253** gave the amidines **254**, which were cyclized to the phenyl-substituted tricycles **255** by heating in concentrated hydrochloric acid.²⁷⁸



²⁷⁴ I. Hermecz, J. Kókósi, L. Vasvári-Debreczy, Á. Horváth, T. Breining, and C. DeVos, unpublished results.

²⁷⁵ R. Y. Ning, J. F. Blount, W. Y. Chem, and P. B. Madan, *J. Org. Chem.* **40**, 2201 (1975).

²⁷⁶ M. Wamhoff and L. Lichtenthaeler, *Chem. Ber.* **111**, 2813 (1978).

²⁷⁷ V. I. Shvedov, I. A. Kharizomenova, L. B. Altukhova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 428 (1970) [*CA* **73**, 25403 (1970)].

²⁷⁸ F. Ishikawa, A. Kosayama, and K. Abiko, *Japan Kokai* 78/44,592 [*CA* **98**, 109566 (1978)].

3. From Δ^1 -Azacycloalkenes with 2-Aminobenzaldehyde

Reaction of the Δ^1 -azacycloalkenes **256** with 2-aminobenzaldehyde afforded the tricyclic salts **257**. This reaction has been widely used for the identification and determination of various naturally occurring compounds (e.g., diamines) in biological and biochemical media.

The Δ^1 -azacycloalkenes **256** as starting materials are applied directly^{279–283} or are formed *in situ* from tripyrroline²⁸⁴; from tripiperidines^{285–289} and isotripiperidine^{285–288} by dissociation, from D-xylopiperidinose by elimination of water²⁹⁰; from 1, ω -diaminoalkanes by enzymatic oxidation^{291–295}; from ω -acetamidoalkan-1-ones with deacylase²⁹⁶; from α -amino adipic acid by enzymatic reduction²⁹⁷; and from proline by oxidation^{298,299} via ω -aminoalkan-1-ones.^{292,300–306}

²⁷⁹ K. Osugi, *J. Pharm. Soc. Jpn.* **78**, 1332 (1958).

²⁸⁰ K. Osugi, *J. Pharm. Soc. Jpn.* **78**, 1355 (1958).

²⁸¹ L. Skursky, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **14B**, 473 (1959).

²⁸² G. Di Maio and P. A. Tardella, *Gazz. Chim. Ital.* **94**, 578 (1964).

²⁸³ G. Adam, *Chem. Ber.* **101**, 1 (1968).

²⁸⁴ A. Luttringhaus, J. Jander, and R. Schneider, *Chem. Ber.* **92**, 1756 (1959).

²⁸⁵ C. Schöpf, A. Komzak, F. Braun, E. Jacobi, M. L. Bornuth, M. Bullnheimer, and I. Hagel, *Justus Liebigs Ann. Chem.* **559**, 1 (1948).

²⁸⁶ C. Schöpf, H. Arm, and H. Krimm, *Chem. Ber.* **84**, 690 (1951).

²⁸⁷ C. Schöpf, H. Arm, and F. Braun, *Chem. Ber.* **85**, 937 (1952).

²⁸⁸ C. Schöpf, F. Braun, and K. Otte, *Chem. Ber.* **86**, 918 (1953).

²⁸⁹ C. Schöpf and K. Otte, *Chem. Ber.* **89**, 335 (1956).

²⁹⁰ H. Paulsen, F. Leupold, and K. Todt, *Justus Liebigs Ann. Chem.* **692**, 200 (1966).

²⁹¹ K. Hasse and H. Maisack, *Biochem. Z.* **328**, 429 (1957).

²⁹² K. Hasse and H. Maisack, *Biochem. Z.* **327**, 296 (1955).

²⁹³ W. B. Jakoby and J. Fredricks, *J. Biol. Chem.* **234**, 2145 (1959).

²⁹⁴ L. Macholan, *Collect. Czech. Chem. Commun.* **31**, 2167 (1966).

²⁹⁵ J. C. Richards and I. D. Spencer, *Tetrahedron* **39**, 3549 (1983).

²⁹⁶ K. Hasse and G. Schmid, *Biochem. Z.* **337**, 480 (1963).

²⁹⁷ F. Konek, *Math. Naturwiss. Ber. Ungarn* **54**, 452 (1936) [*CA* **31**, 5367g (1937)].

²⁹⁸ L. Skursky, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **14B**, 474 (1959).

²⁹⁹ S. Johné and D. Gröger, *Z. Chem.* **5**, 228 (1965).

³⁰⁰ C. Schöpf and E. Oechler, *Justus Liebigs Ann. Chem.* **523**, 1 (1936).

³⁰¹ C. Schöpf, *Angew. Chem.* **50**, 779, 797 (1937).

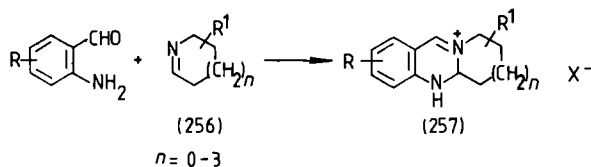
³⁰² N. J. Leonard and M. J. Martell, *Tetrahedron Lett.*, 44 (1960).

³⁰³ S. Sakamoto and K. Samejima, *Chem. Pharm. Bull.* **27**, 2220 (1979).

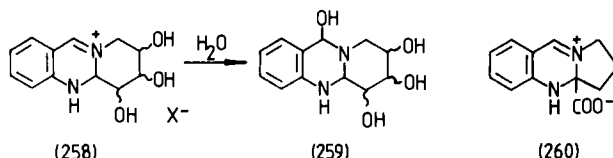
³⁰⁴ S. Sakamoto and K. Samejima, *Koen Yoshiku-Seitai Seibun no Bunseki Kagaku Shinpojumu*, 4th, 120 (1979) [*CA* **92**, 193897 (1980)].

³⁰⁵ L. Skursky, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **15B**, 812 (1960).

³⁰⁶ R. L. Sharma, R. K. Gupta, B. K. Chowdhury, K. L. Dhar, and C. K. Atal, *Indian J. Chem., Sect. B* **18B**, 449 (1979).



When an aqueous solution of the picrate salt **258** was passed through a column of Amberlite IR-45 resin, the stable pseudobase **259** was isolated.²⁹⁰ Cyclocondensation of 5-amino-2-oxopentanoic acid with 2-aminobenzaldehyde yielded the betaine **260**.³⁰⁷



4. From 2-Aminobenzylamines and Their Derivatives

During reduction of the nitro derivatives **261** (with stannous chloride in hydrochloric acid,^{72,308} with hydrogen over Raney nickel in ethanol,³⁰⁹ with iron powder in 50% acetic acid,^{171,310,311} or with triethyl phosphite^{312,313} at 170–180°C), the resulting amino derivatives **262** sometimes underwent spontaneous cyclization and gave the linearly annelated tricyclic compounds **263**. Cyclization of the amino derivatives **262** was effected thermally^{314,315} or by the action of phosphoryl chloride.^{198,316–320}

³⁰⁷ L. Macholán, *Chem. Listy* **51**, 2122 (1957).

³⁰⁸ S. Gabriel, *Chem. Ber.* **45**, 713 (1912).

³⁰⁹ A. M. Downes and F. Lions, *J. Am. Chem. Soc.* **72**, 3053 (1950).

³¹⁰ P. L. Southwick and J. Casanova, Jr., *J. Am. Chem. Soc.* **80**, 1168 (1958).

³¹¹ P. L. Southwick and S. E. Cremer, *J. Org. Chem.* **24**, 753 (1959).

³¹² T. Kametani, K. Niyu, and T. Yamanaka, *J. Pharm. Soc. Jpn.* **92**, 1184 (1972).

³¹³ T. Kametani, K. Niyu, and T. Yamanaka, Japan Kokai 74/76,899 [*CA* **82**, 16857 (1975)].

³¹⁴ E. Späth, F. Kuffner, and N. Platzer, *Chem. Ber.* **68**, 699 (1935).

³¹⁵ E. Späth and N. Platzer, *Chem. Ber.* **69**, 387 (1936).

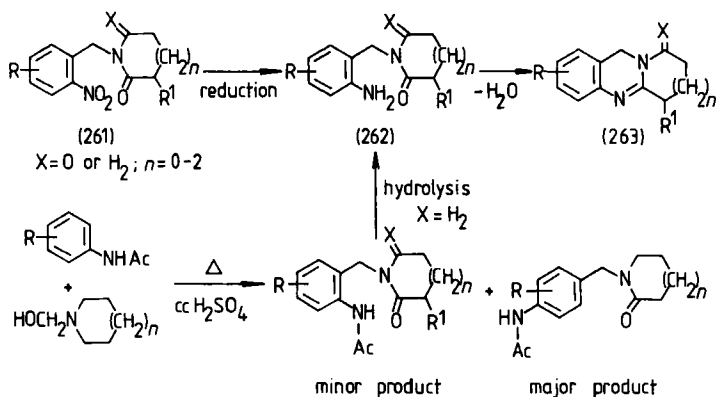
³¹⁶ E. Späth, F. Kuffner, and N. Platzer, *Chem. Ber.* **68**, 497 (1935).

³¹⁷ Kh. M. Shakhidoyatov, A. Irisbaev, and Ch. Sh. Kadyrov, *Khim. Geterotsikl. Soedin.*, 834 (1975) [*CA* **83**, 192982 (1975)].

³¹⁸ A. Irisbaev, Kh. M. Shakhidoyatov, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 531 (1975) [*CA* **84**, 4894 (1976)].

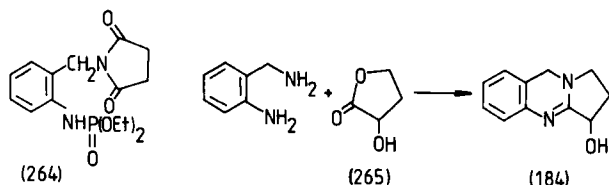
³¹⁹ A. Irisbaev, Kh. M. Shakhidoyatov, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 809 (1975) [*CA* **84**, 150823 (1976)].

³²⁰ Kh. M. Shakhidoyatov, A. Irisbaev, and A. P. Abdulaev, *Regul. Rosta Rast. Gerbitsidy, Tashkent*, 166 (1978) [*CA* **91**, 91588 (1979)].



Cyclization of compound **262** ($\text{R} = \text{R}^1 = \text{H}$, $\text{X} = \text{H}_2$, $n = 0$) failed,³²¹ but its hydroxy derivative ($\text{R}^1 = \text{OH}$) could be cyclized thermally.³¹⁴

In the reduction of the nitro derivative **261** ($\text{R} = \text{R}^1 = \text{H}$, $\text{X} = \text{O}$, $n = 0$) with triethyl phosphite, the *N*-(2-diethylphosphoramidobenzyl)succinimide **264** was also formed.³¹²



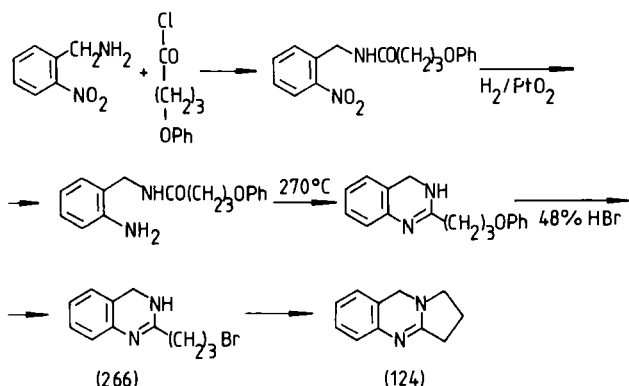
While the reaction of 2-aminobenzylamine with 3-hydroxy- γ -butyrolactone (**265**) at 200°C under a nitrogen atmosphere gave 3-hydroxytetrahydropyrrolo[2,1-*b*]quinazoline (**184**) directly, the reaction with γ -butyrolactone yielded 2-(3-hydroxypropyl)-3,4-dihydroquinazoline (**122**).³²² Compound **122** was cyclized⁵⁷ with phosphoryl chloride to a 1 : 2 mixture of the linear isomer **124** and the angular isomer **123** (see Section IV, A, 1).

Hanford and Adams³²¹ stated that cyclization of 2-(3-bromopropyl)dihydroquinazoline (**266**) by means of alkali afforded only the linear isomer **124**. Compound **266** was prepared from 2-nitrobenzylamine and phenoxybutyryl chloride, as shown below:

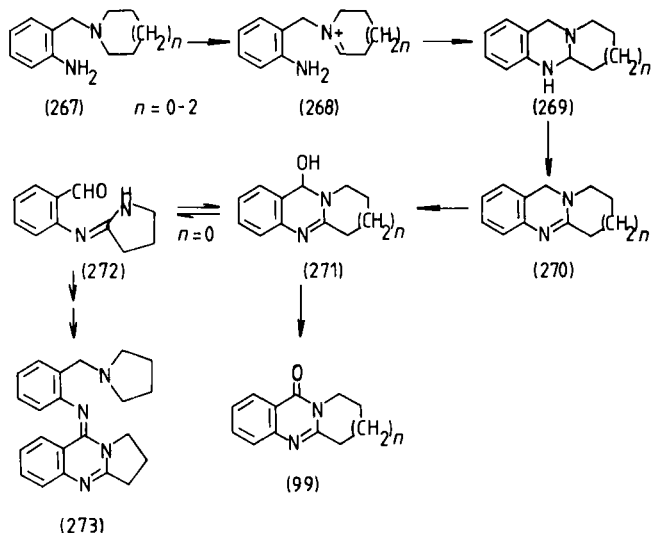
Suschtzky and Meth-Cohn¹⁹⁹ reported the oxidation of the 2-aminobenzylamines (**267**) with manganese dioxide in benzene at room temperature. The six- and seven-membered homologs **267** ($n = 1, 2$) gave rise to the tricyclic products **99** ($n = 1, 2$) in 19 and 71% yields, respectively. The

³²¹ W. E. Hanford and R. Adams, *J. Am. Chem. Soc.* **57**, 921 (1935).

³²² E. Späth and N. Platzer, *Chem. Ber.* **69**, 255 (1936).

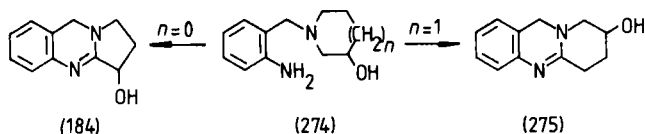


five-membered homolog **267** ($n = 0$) afforded product **273**. The following reaction mechanism was proposed. Oxidation of the α -methylene group of the heterocyclic ring leads to the iminium salt **268**, which undergoes ring closure to **269** and dehydrogenation to **270**. Oxidation of the methylene group of the pyrimidine ring of **270** leads via the aminocarbino **271** to the final product **99**.



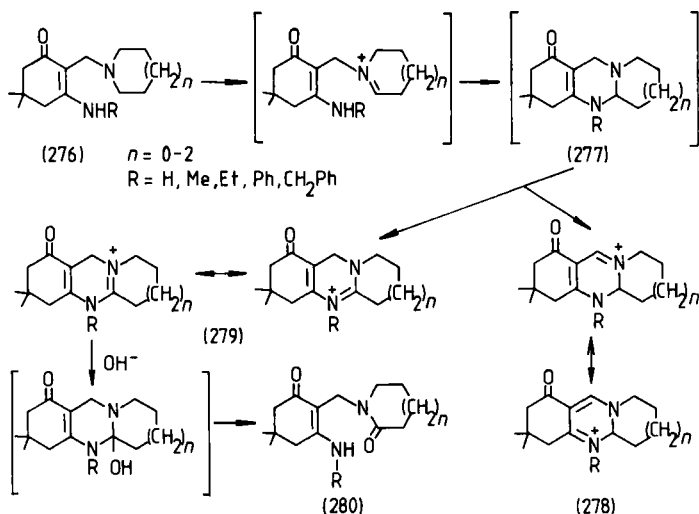
Compound **273** probably arises from the anil condensation between the starting amine **267** ($n = 0$) and the aminoaldehyde tautomer **272** of the aminocarbinal **271** ($n = 0$). The aldehyde form (**272**) is probably more favored in the five-membered ring system than in the corresponding six- and seven-membered homologs. Recyclization and oxidation to **273** complete the process.

Möhrle and Gundlach^{323,324} carried out the oxidative cyclization of the 2-aminobenzylamines **267** with the mercuric acetate–EDTA reagent to obtain the nitrogen bridgehead compounds **270** in 64–80% yields. The oxidation of the tricyclic compounds **270** with manganese dioxide produced the corresponding fused quinazolinones **99**.³²⁴



The five-membered hydroxy derivative **274** ($n = 0$) produced the 3-hydroxypyrrolo[2,1-*b*]quinazoline **184**^{324,325} while the six-membered homolog gave the isomeric **275**³²⁴ on oxidation with the mercuric acetate–EDTA reagent.

Möhrle and Herbke^{326–328} studied the oxidation of the aminocyclohexenones **276** with the mercuric acetate–EDTA reagent. The primarily formed tricyclic compounds **277** may undergo further oxidation in two positions of the molecule and give compound **278** or/and **279** and **280**. Compound **279** ($R = H$) is easily hydrolyzed to the lactams **280**.³²⁶



³²³ H. Möhrle and P. Gundlach, *Tetrahedron Lett.*, 997 (1970).

³²⁴ H. Möhrle and P. Gundlach, *Arch. Pharm. (Weinheim, Ger.)* **306**, 541 (1973).

³²⁵ H. Möhrle and P. Gundlach, *Tetrahedron Lett.*, 3249 (1970).

³²⁶ H. Möhrle and J. Herbke, *Chem.-Ztg.* **103**, 266 (1979).

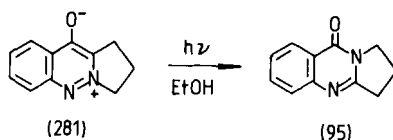
³²⁷ H. Möhrle and J. Herbke, *Monatsh. Chem.* **111**, 627 (1980).

³²⁸ H. Möhrle and J. Herbke, *Pharmazie* **35**, 389 (1980).

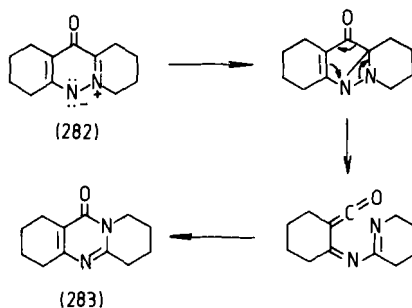
The five-membered homologs **276** ($n = 0$) yielded compounds **280** ($n = 0$) when $R = \text{Et}$, Ph , or PhCH_2 , but the pyrrolo[2,1-*b*]quinazoline **279** ($n = 0$) when $R = \text{H}$. From the methyl derivative of **276** ($n = 0$, $R = \text{Me}$), both the tricyclic compound **279** ($n = 0$) and the lactam **280** ($n = 0$) were obtained. The six-membered homologs **276** ($n = 1$) gave compounds **278** ($n = 1$) when $R = \text{H}$, Me , or PhCH_2 , whereas derivatives in which $R = \text{Et}$ or Ph afforded both the pyrido[2,-1-*b*]quinazolines **278** ($n = 0$) and the lactams **280** ($n = 1$). The seven-membered homologs **276** ($n = 2$) gave compound **279** ($n = 2$) if $R = \text{H}$, and compound **278** if $R = \text{Me}$, Et , or PhCH_2 .

5. By Ring Transformations

On irradiation of the zwitterionic pyrrolo[1,2-*b*]cinnoline **281** in ethanol, Ames *et al.*³²⁹ obtained the pyrrolo[2,1-*b*]quinazolinone **95**.

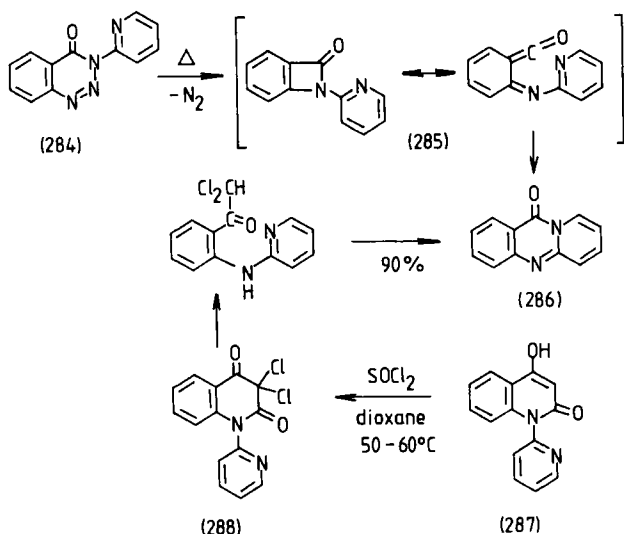


Ning *et al.*²⁷⁵ described the photoisomerization of the zwitterionic pyrido[1,2-*b*]cinnoline **282** to the octahydropyrido[2,1-*b*]quinazoline **283**.



Smalley and co-workers²⁴⁰ obtained the pyrido[2,1-*b*]quinazolin-11-one **286** through the thermal decomposition of 3-(2-pyridyl)-1,2,3-benzotriazin-4-one (**284**) in 1-methylnaphthalene. The pyrido[2,1-*b*]quinazolinone **286** probably arises from the benzazetinone-iminoketene intermediate **285**. Photodecomposition of the benzotriazinone **284** in tetrahydrofuran was very slow. Irradiation for 72 hr furnished the pyridoquinazolinone **286** in less than 5% yield along with the unchanged benzotriazinone **284**.

³²⁹ D. E. Ames, S. Chandrasekhav, and R. Simpson, *J. C. S. Perkin I*, 2035 (1975).



Kappe and Lube²²⁸ synthesized the pyrido[2,1-*b*]quinazolinone **286** in 90% yield by treating the 3,3-dichloroquinoline-2,4-dione **288** with sodium carbonate in aqueous ethanol at ambient temperature. Compound **288** was prepared from the quinoline **287**.

6. Miscellaneous Syntheses

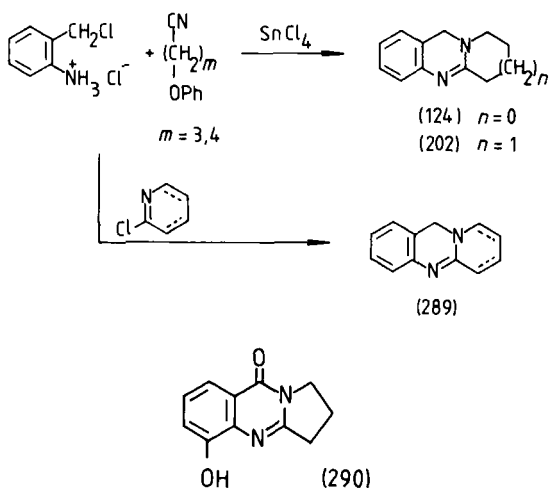
By treating *o*-chloromethylaniline hydrochloride with ω -benzyloxybutyro- and -valeronitriles in refluxing *o*-dichlorobenzene in the presence of stannic chloride, Muñoz and Madroñero¹⁹⁷ obtained the tricyclic compounds **124** and **202**, respectively. The pyrido[2,1-*b*]quinazolines **289** were prepared by refluxing *o*-chloromethylaniline hydrochloride in dichlorobenzene with 2-chloropyridine and its tetrahydro derivative. The latter was obtained *in situ* by Beckmann rearrangement of cyclopentanone oxime with phosphorus pentachloride.

Klebsiella pneumoniae oxytoca produces 2,3-dihydro-5-hydroxypyrrolo[2,1-*b*]quinazolin-9-one (**290**) and 3-hydroxyanthranilic acid.¹⁸⁵ These compounds are believed to be responsible for the brown color of *K. pneumoniae oxytoca* cultures on agar plates.

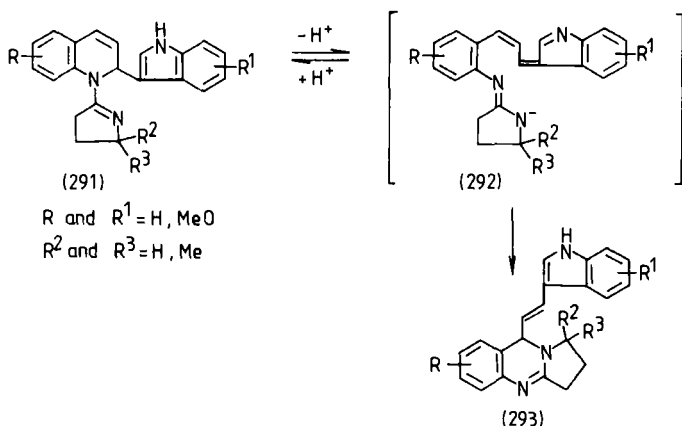
Ryan *et al.*^{330,331} reported that the 2-(3-indolyl-1-(1-pyrrolin-2-yl)quinolines **291** rearranged to the (3-indolylvinyl)pyrrolo[2,1-*b*]quinazolines **293**

³³⁰ R. P. Ryan, R. A. Hamby, C. M. Combs, and Y. H. Wu, *J. Org. Chem.* **40**, 728 (1975).

³³¹ R. P. Ryan, U.S. Patent 3,853,858 [*CA* **82**, 171014 (1975)].



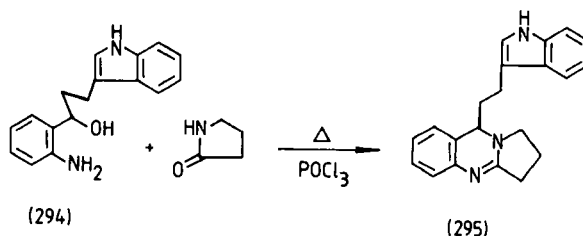
in a general base-catalyzed process. The primary event leading to rearrangement is the abstraction of the indolic NH proton by a base to give the ring-opened intermediate **292**. The rearrangement did not proceed when the indole nitrogen was methylated.



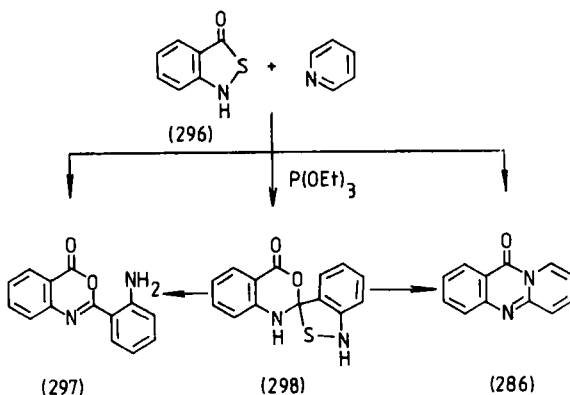
3-[3-(2-Aminophenyl)-3-hydroxypropyl]indole (**294**) and pyrrolidinone in refluxing 1,2-dichloroethane in the presence of phosphoryl chloride gave 9-(3-indolyethyl)pyrrolo[2,1-*b*]quinazoline (**295**).³³⁰

Davis *et al.*³³² found that the reaction between 1,2-benzisothiazolin-3(1*H*)-one (**296**) and triethyl phosphite in pyridine at ambient temperature

³³² M. Davis, R. J. Hook, and W. Y. Wu, *J. Heterocycl. Chem.* **21**, 369 (1984).



resulted in a mixture containing not only the starting compound **296** and poly(anthraniloyl)benzoxazinone, but also the benzoxazine **297**, the *N*-dianthraniloyl derivative of the benzoxazinone **297**, the spiro compound **298**, and the pyrido[2,1-*b*]quinazolinone **286**. The nitrogen bridgehead compound **286** was isolated in 5% yield.

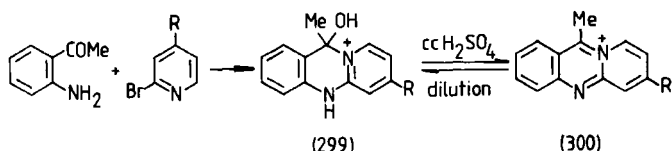


Further reaction of the spiro compound **298** with pyridine and triethyl phosphite produced an additional amount of the benzoxazine **297**, its *N*-dianthraniloyl derivative, poly(anthraniloyl)benzoxazinone and the pyrido[2,1-*b*]quinazolinone **286**.

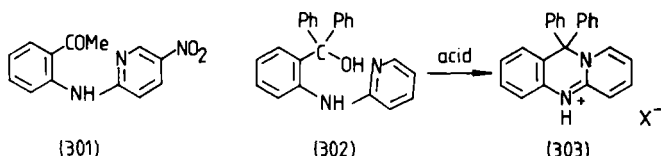
The pyrido[2,1-*b*]quinazolinone **286** could be produced in about 20% yield by simply boiling a solution of benzisothiazolinone (**296**) in aqueous pyridine for 6 hr.³³² Pyrido[2,1-*b*]quinazolinone (**286**) formation can be interpreted by a mechanism in which nucleophilic attack of the pyridine nitrogen atom occurs on the carbonyl group of benzisothiazolinone (**296**).

The acid-catalyzed condensation of 2-bromopyridines with *o*-aminoacetophenone in dilute acids afforded the pseudobases **299**.³³³ These pseudobases underwent dehydration in concentrated sulfuric acid to give the pyrido[2,1-*b*]quinazolinium salts **300**, but on dilution of the acid covalent hydration occurred, causing reversion to the pseudobases.

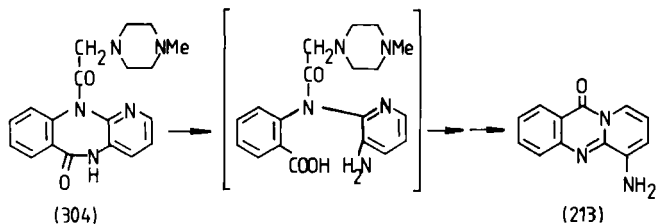
³³³ C. K. Bradsher, R. W. L. Kimber, and S. D. Mills, *J. Org. Chem.* **30**, 1539 (1965).



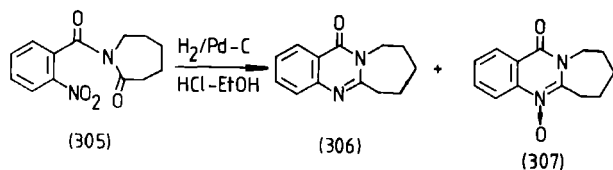
2-Bromo-5-nitropyridine gave only the condensation product **301**. Bradsher *et al.*³³³ cyclized the diphenyl carbinol **302** to the 9,9-diphenylpyrido[2,1-*b*]quinazolinium halides **303** by heating in acid.



6-Aminopyrido[2,1-*b*]quinazolinone (**213**) was formed when the anti-ulcer agent pirenzepine (**304**) was heated under alkaline or acidic conditions.²⁴²



Suschtzky and co-workers³³⁴ hydrogenated the lactam **305** over palladium on charcoal under pressure in the presence of 1 molar equivalent of hydrochloric acid in ethanol at room temperature and observed the formation of the azepino[2,1-*b*]quinazolinone **306** and its *N*-oxide **307** in yields of 12 and 69%, respectively.

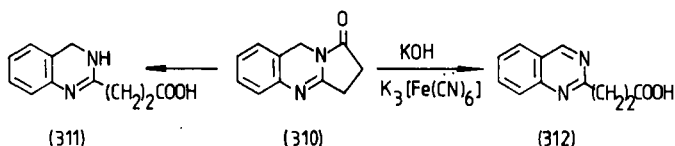
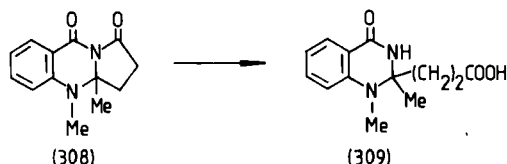


³³⁴ R. Fielden, O. Meth-Cohn, and H. Suschtzky, *J. C. S. Perkin I*, 702 (1973).

C. REACTIONS

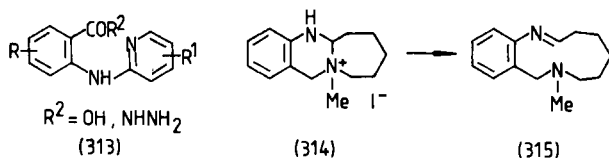
1. Hydrolysis and Ring Opening

Alkaline hydrolysis of the hexa- and tetrahydropyrrolo[2,1-*b*]quinazolin-1-ones **308** and **310** afforded the respective tetra- and dihydroquinazoline-2-propionic acids (**309** and **311**).^{36,308} In the presence of potassium ferricyanide in aqueous potassium hydroxide, the tetrahydropyrrolo[2,1-*b*]quinazolin-1-one **310** gave the quinazoline-2-propionic acid **312**.³⁰⁸



By the action of alcohol or amine, the pyrrolo[2,1-*b*]quinazoline-1,9-dione **241** underwent a facile ring opening to give the corresponding 2-substituted quinazolinone **243**.¹⁹⁶

The pyrido[2,1-*b*]quinazolin-1-ones **211** exhibit ring opening by the action of alkali^{216,218,241,259,335-337} or hydrazine hydrate^{214,338} at 100–120°C and give the *N*-arylanthranilic acids **313** ($R^2 = \text{OH}$) and the hydrazides **313** ($R^2 = \text{NHNH}_2$), respectively.



³³⁵ K. Schromm, A. Mentrup, E. D. Renth, A. Fuegner, and V. Jacobi, German Patent 2,735,919 [CA 91, 39518 (1979)].

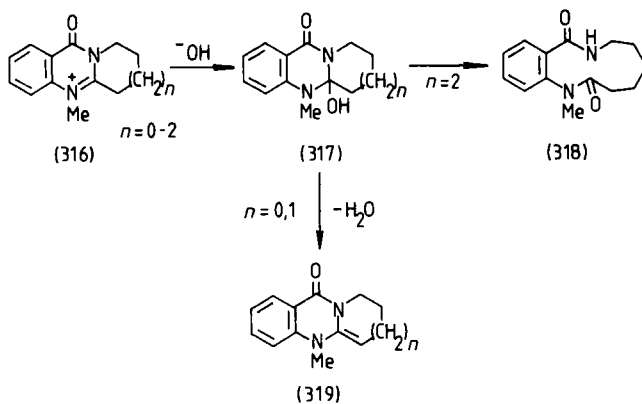
³³⁶ Ch. F. Schwender and B. R. Sunday, U.S. Patent 4,179,509 [CA 92, 163849 (1980)].

³³⁷ K. Schromm, A. Mentrup, E. O. Renth, and A. Fuegner, European Patent Appl. 56,114 [CA 97, 182222 (1982)].

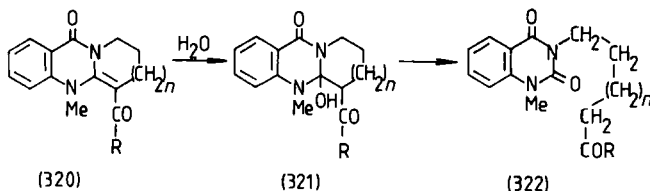
³³⁸ C. R  th, *Justus Liebigs Ann. Chem.* **486**, 284 (1931).

When the quaternary salt **314** was treated with aqueous sodium hydroxide, the [1,8]benzodiazacycloundecine **315** was obtained.³³⁹

Depending on the reaction conditions, treatment of the quaternary salts **316** with alkali afforded the ring-opened product **318**²⁰³ or the relatively unstable enamines **319**^{181,201,202,340} via the azacyclols **317**. Rothe *et al.*³⁴⁰ succeeded in isolating the azacyclol **317** ($n = 0$) from the five-membered homolog **316** ($n = 0$). The azacyclol **317** ($n = 0$) was then dehydrated to the enamine **319** ($n = 0$).³⁴⁰



The C-acyl compounds **320** underwent hydration on being heated in aqueous alcohol, but the resulting unstable azacyclols **321** underwent retroaldol fission and afforded the ring-opened derivatives **322**.^{181,201} When the reaction was carried out in deuterium oxide or in labeled water, the incorporation of deuterium in the position α to the RCO group or of ^{18}O into the ureido carbonyl group was observed.^{181,201}

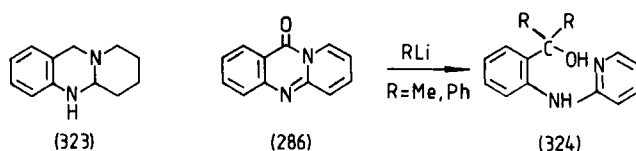


Acidic hydrolysis of nordine (**201**) afforded vasicine (**184**),¹⁷⁶ while that of the pyrrolo[2,1-*b*]quinazoline **273** gave the pyrrolo[2,1-*b*]quinazolinone **95**.¹⁹⁹

³³⁹ L. Brzechffa, M. K. Eberle, and G. G. Kahle, *J. Org. Chem.* **40**, 3062 (1975).

³⁴⁰ M. Rothe, T. Tóth, and D. Jacob, *Angew. Chem., Int. Ed. Engl.* **10**, 128 (1971).

Acetylation of the pyrido[2,1-*b*]quinazoline **323** resulted in ring cleavage.¹⁷⁹

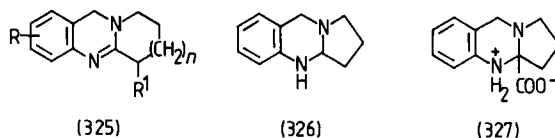


Bradsher *et al.*³³³ found that treatment of the 11*H*-pyrido[2,1-*b*]quinazolin-11-one **286** with excess organolithium reagent gave the tertiary carbinol **324**.

Other reactions leading to ring cleavage are mentioned in Sections V,B,1, B,6, and C,2.

2. Hydrogenation and Reduction

In a strong hydrogen current in the presence of palladium sponge or palladium on barium sulfate at 25–100°C, the quaternary salts **257** were converted to compounds **325**.^{281,299–302,306} Adams platinum oxide and Raney nickel were also used.²⁸¹

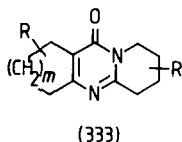
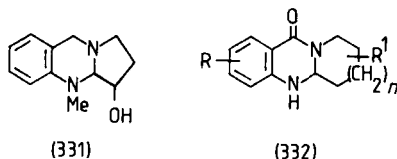
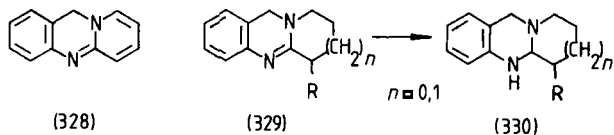


At lower temperature, with a smaller amount of catalyst (Pd–BaSO₄) and 1 molar equivalent of hydrogen, the five-membered derivatives **257** (R = R¹ = H, *n* = 0) gave the hexahydropyrrolo[2,1-*b*]quinazoline **326**.²⁸¹ Hydrogenation of the betaine **260** over palladium on barium sulfate yielded the hexahydro derivative **327**.³⁰⁷

The 11*H*-pyrido[2,1-*b*]quinazoline hydroiodide **328**·HI was hydrogenated over platinum(IV) oxide in ethanol to the tetrahydro derivative **202**.¹⁹⁷ Under similar conditions the base **328** afforded the hexahydro derivative **323**.¹⁹⁷

Compounds **330** were prepared by saturation of the C=N bond of the tricyclic compounds **329** by hydrogenation over palladium on activated carbon,¹⁷⁹ or by reduction with sodium borohydride¹⁷⁹ or sodium in alcohol.^{197,198,316} Reduction of the tetrahydropyrrolo[2,1-*b*]quinazolin-1-one **310** with sodium in amyl alcohol yielded the hexahydropyrrolo[2,1-*b*]quinazoline **330** (R = H, *n* = 0).³¹⁵ Reduction of the 3-hydroxypyr-

pyrrolo[2,1-*b*]quinazoline **184** with sodium in isoamyl alcohol gave a mixture of the hexahydro compound **330** ($R = H$, $n = 0$) and its hydroxy derivative **330** ($R = OH$, $n = 0$).³⁴¹ When **184** was reduced with sodium borohydride, not only **330** ($R = OH$; $n = 0$), but also the ring-cleaved product **274** ($n = 0$) was obtained.³⁴² If the methiodide of **184** was reduced with sodium borohydride in methanol, only the hexahydro product **331** was formed.³⁴³



The *N*-(*o*-aminobenzyl)pyrrolidine **267** ($n = 0$) was obtained from the pyrrolo[2,1-*b*]quinazolines **124** and **186** with sodium borohydride.³⁴²

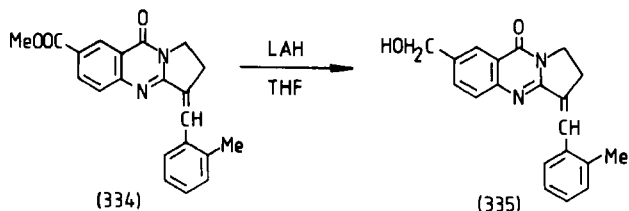
Compounds **330** were also prepared from **205** by reduction with lithium aluminum hydride.^{40,57,106,339} When reduction was carried out with sodium borohydride, only the $C=N$ bond was saturated and compounds **332** were formed.^{271,342} The carbonyl group of compounds of type **332** was reduced by lithium aluminum hydride to give compounds of type **330**.⁴⁰ The $C=N$ bond of compounds of type **333** could not be reduced with sodium borohydride or by catalytic hydrogenation over palladium or Raney nickel.²⁶⁶

The methoxycarbonyl group of the pyrrolo[2,1-*b*]quinazolone **334** was reduced to a hydroxymethyl group with lithium aluminum hydride in tetrahydrofuran at $0^\circ C$.²¹⁰

³⁴¹ E. Späth, F. Kuffner, and N. Platzer, *Chem. Ber.* **68**, 935 (1935).

³⁴² B. Kh. Zharekeev, M. V. Telezhenetskaya, Kh. N. Khashimov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 679 (1974) [*CA* **82**, 73290 (1975)].

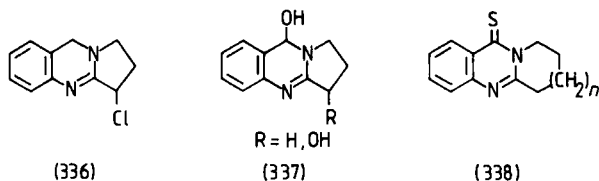
³⁴³ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **75**, 4474 (1953).



The hexahydropyrrolo[2,1-*b*]quinazolinone **332** ($R = R^1 = H$, $n = 0$) was obtained when the pseudobase **317** ($n = 0$) was hydrogenated over palladium.³⁴⁰

The carbonyl group of tricyclic compounds of type **99** was reduced to a methylene group with zinc powder in acetic acid^{57,179,190,197,198,254} or hydrochloric acid,^{106,189,191,193,194,344} to give compounds **329** ($n = 0-3$). If compounds of type **99** contained a hydroxy group^{106,254} or a halogen atom(s)^{191,254,344} on the methylene group adjacent to the $C=N$ bond, or an iodo atom on the sp^2 carbon atom,¹⁹¹ these groups too were eliminated during reduction with zinc. On reduction with zinc powder in 10% hydrochloric acid at ambient temperature for 8 hr, the 3-hydroxytetrahydropyrrolo[2,1-*b*]quinazolin-9-one **185** afforded a 1 : 4 mixture of the tetrahydropyrrolo[2,1-*b*]quinazoline **124** and the tetrahydropyrrolo[2,1-*b*]quinazolin-9-one **95**. The 3-chlorotetrahydropyrrolo[2,1-*b*]quinazoline **336** yielded the tetrahydropyrrolo[2,1-*b*]quinazoline **124** by the action of zinc powder in acidic medium.^{316,321,345} Polarographic reduction of pyrrolo[2,1-*b*]quinazolin-9-ones **95** and **185** gave the corresponding 9-hydroxy derivatives **337**.³⁴⁶

The thiocarbonyl group of the tricyclic compounds **338** was converted to a methylene group with zinc in hydrochloric acid³⁴⁷ or by the action of Raney nickel,⁵⁷ and desulfurized derivatives of type **329** were formed.



³⁴⁴ Kh. M. Shakhidoyatov, A. Irisbaeva, E. Oripov, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 557 (1976) [*CA* **85**, 192957 (1976)].

³⁴⁵ T. P. Ghose, *J. Indian Chem. Soc.* **4**, 1 (1928).

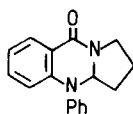
³⁴⁶ E. K. Dobronravova, M. V. Telezhenetskaya, and T. T. Shakirov, *Khim. Prir. Soedin.*, 363 (1976) [*CA* **85**, 130572 (1976)].

³⁴⁷ Kh. M. Shakhidoyatov and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 668 (1977). [*CA* **88**, 105627 (1978)].

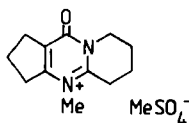
Späth and Kuffner²⁰⁰ obtained the tetrahydropyrido[2,1-*b*]quinazolinone **203** when the pyrido[2,1-*b*]quinazolinone **286** was hydrogenated over palladium on carbon in acetic acid. By means of hydrogenation in ethanol for 4 days, Paterson *et al.*²⁴⁰ prepared the hexahydropyrido[2,1-*b*]quinazolinone **102**.

Reduction of compounds **244** over palladium on carbon or on Raney nickel gave compounds **333**.^{187,217,246,266}

Reduction of the quaternary salt **327** with sodium borohydride yielded the 4-phenylhexahydropyrrolo[2,1-*b*]quinazolinone **339**.²⁵⁶ A diastereomeric mixture of perhydro derivatives was obtained when the methosulfate **340** was reduced with sodium borohydride.^{246,347}

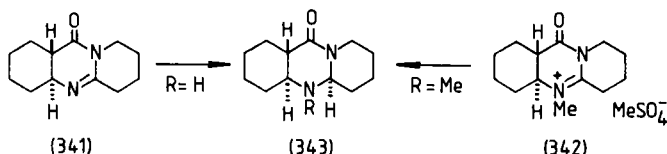


(339)



(340)

Bernáth, Fülöp and co-workers^{246-248,348-350} studied the reduction of compounds of types **224** and **225**. On reduction with sodium borohydride in methanol or by hydrogenation over platinum oxide in ethanol or acetic acid, the *trans*-decahydropyrido[2,1-*b*]quinazolinone **341** and its quaternary derivative **342** gave exclusively the perhydro derivative **343**.^{349,350}



(341)

(343)

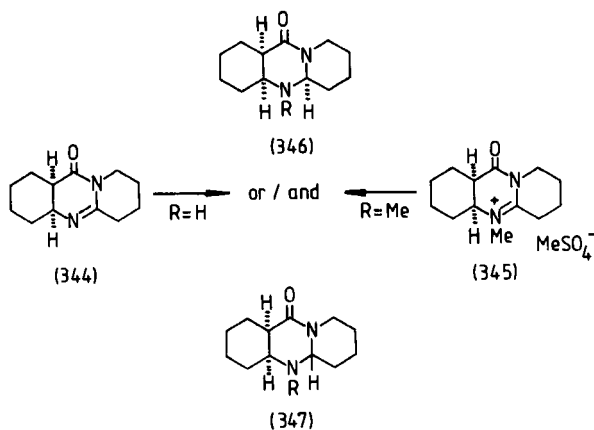
(342)

The *cis* derivative **344** afforded the perhydro compound **346** by reduction with sodium borohydride and by hydrogenation over platinum oxide in ethanol.^{349,350} However, if the catalytic reduction of the *cis* derivative **344** was carried out in acetic acid, a 3 : 1 mixture of the diastereomeric perhydro compounds **346** and **347** was obtained.^{349,350} Reduction of the quaternary *cis* compound **345** resulted in a mixture of the diastereomeric perhydro derivatives **346** and **347**, with a predominance of the latter.^{349,350}

³⁴⁸ F. Fülöp, I. Huber, G. Bernáth, G. Tóth, K. Simon, I. Hermecz, and Z. Mészáros, *Heterocycles* **21**, 678 (1984).

³⁴⁹ F. Fülöp, K. Simon, G. Tóth, I. Hermecz, Z. Mészáros, and G. Bernáth, *J. C. S. Perkin I*, 2801 (1982).

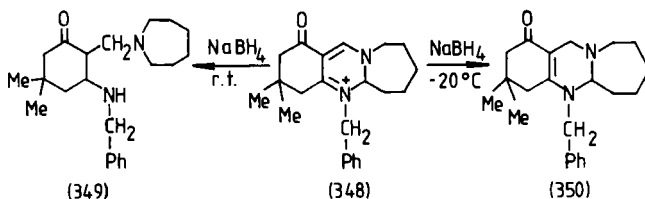
³⁵⁰ F. Fülöp, G. Bernáth, K. Simon, I. Hermecz, Z. Mészáros, and G. Tóth, *Magy. Kem. Foly.* **89**, 281 (1983) [*CA* **100**, 51535 (1984)].



Aniflorine (197) yielded deoxyaniflorine (198) on being treated with Raney nickel in ethanol under a hydrogen atmosphere for 4 days.¹²⁴

The azepino[2,1-*b*]quinazolinone *N*-oxide 307 was deoxygenated to the azepino[2,1-*b*]quinazolinone 306 upon irradiation of its methanolic solution for 96 hr.³³⁴

Reduction of the azepino[2,1-*b*]quinazolinone 348 with sodium borohydride in methanol led to the ring-opened product 349 at ambient temperature and to the azepino[2,1-*b*]quinazolinone 350 at -20°C .³²⁸



The electrolytic reductions of the tetrahydropyrrolo[2,1-*b*]quinazolin-1- and -9-ones 310 and 95 and of vasicine (184) on a lead cathode were studied by Narang and co-workers^{72,351-354} and Späth and Platzer.^{198,315}

Späth and Platzer obtained 1-(*o*-aminobenzyl)pyrrolidine (353) from both tetrahydropyrrolo[2,1-*b*]quinazolinones (95 and 310).^{198,315} Narang and Ray found that 310 yielded not only 353 but also the hexahydropyrrolo[2,1-*b*]quinazolin-1-one 354, while from vasicine (184) the pyrido-

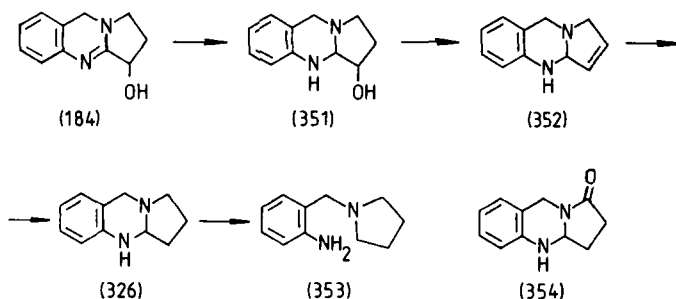
³⁵¹ J. N. Răy, K. S. Narang, and H. R. Juneja, *Curr. Sci.* **3**, 352 (1935).

³⁵² K. S. Narang and J. N. Răy, *Curr. Sci.* **3**, 552 (1935).

³⁵³ K. S. Narang and J. N. Răy, *J. Chem. Soc.*, 686 (1936).

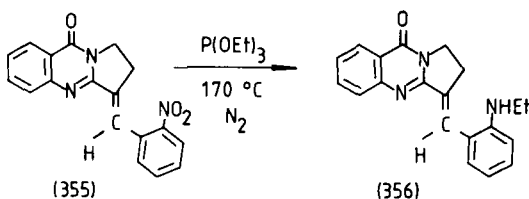
³⁵⁴ K. S. Narang and J. N. Răy, *J. Chem. Soc.*, 1570 (1936).

[2,1-*b*]quinazolines **326**, **351**, and **352** could also be prepared, depending on the reaction period.³⁵³



The nitro group attached to an sp^2 carbon in compounds **205**, **211**, and **244** and to the phenyl ring of compounds such as **334** was reduced to an amino group with iron powder,^{191,246,266,344} tin^{183,213} and tin(II) chloride dihydrate^{210,268,355} in hydrochloric acid and/or acetic acid medium, or by catalytic hydrogenation over palladium on carbon in ethanol.^{304,356}

The nitro group of the benzal derivative **355** was converted to an ethyl-amino group by reduction with triethyl phosphite at 170°C under a nitrogen atmosphere for 20 hr.^{357,358}



3. Dehydrogenation and Oxidation

Dehydrogenation of the tetrahydropyrido[2,1-*b*]quinazolinone **203** over palladium sponge at 275°C afforded the pyrido[2,1-*b*]quinazolinone **286**.²⁰⁰

Dehydrogenation of compounds **332** ($R = R^1 = \text{H}$, $n = 0, 1$) with the mercuric acetate–EDTA complex yielded compounds **99** ($n = 0, 1$) in high yields.³⁵⁹

³⁵⁵ G. Doria, C. Passarotti, and M. L. Corno, German Patent 3,326,511 [*CA* **101**, 7185 (1984)].

³⁵⁶ S. Sakamoto and K. Samejima, *Chem. Pharm. Bull.* **28**, 916 (1980).

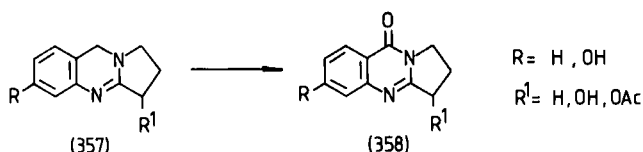
³⁵⁷ T. Kametani, T. Yamanaka, and K. Nyu, *J. Heterocycl. Chem.* **9**, 1281 (1972).

³⁵⁸ T. Kametani, Japan Kokai 74/85,096 [*CA* **82**, 16864 (1975)].

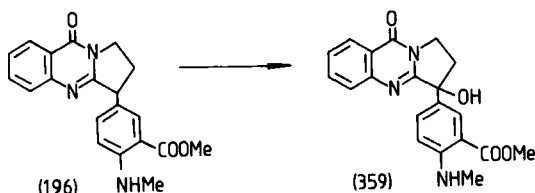
³⁵⁹ H. Möhrle and Ch. M. Seidel, *Arch. Pharm. (Weinheim, Ger.)* **309**, 471 (1976).

The quaternary salts **257** ($R = R^1 = H$, $n = 0, 1$) were oxidized to compounds **99** ($n = 0, 1$) by means of cell-free pea extract^{360,361} or by chromic acid in acidic medium.^{285,300,303,304,362} The betaine **260** gave the tetrahydropyrrolo[2,1-*b*]quinazolin-9-one **95** with 5 molar equivalents of potassium ferricyanide, but the tetrahydropyrrolo[2,1-*b*]quinazolin-9-ol **186** with 2 molar equivalents of potassium ferricyanide.³⁰⁷ The action of potassium ferricyanide converted the hexahydropyrrolo[2,1-*b*]quinazoline-3*a*-carboxylic acid (**327**) to the tetrahydropyrrolo[2,1-*b*]quinazoline **124**.³⁰⁷

The methylene group in the pyrimidine ring of the tetrahydropyrrolo[2,1-*b*]quinazolines **357** was easily oxidized to an oxo group with 30% H_2O_2 in acetone,^{87,90,91,98,106,254,362,363,364} with chromic acid in acetic acid,³⁶⁵ and with atmospheric oxygen.^{57,90,95} The autooxidation was catalyzed by sunlight.^{90,107,180} This autooxidation of compounds **357** ($R = H$) could be prevented by forming the hydrochloride salt.³⁴⁶



The oxidation of anisotine (**196**) with potassium permanganate in acetone at 24°C afforded its 3-hydroxy derivative **359**.¹²⁴



The tetrahydropyrrolo[2,1-*b*]quinazolinone **95** was converted to its 3-hydroxy derivative **185** in 5% yield by treatment with lead tetraacetate in benzene at 50–60°C for 20 hr.²⁵⁴ The hydroxy derivative **185** was also formed by the metabolic oxidation of **95** administered to rats via the intraperitoneal route.³⁶⁶

³⁶⁰ L. Skursky, *Collect. Czech. Chem. Commun.* **30**, 2080 (1965).

³⁶¹ L. Skursky and M. Novotny, *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.*, 577 (1966) [*CA* **67**, 8745 (1967)].

³⁶² S. Sakamoto and K. Samejima, *J. Pharmacobio-Dyn.* **3**, S-24 (1980).

³⁶³ T. Ghose, S. Krishna, K. S. Narang, and J. N. Răy, *J. Chem. Soc.*, 2740 (1932).

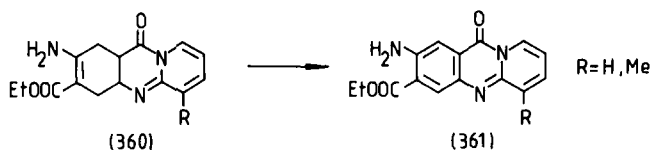
³⁶⁴ T. P. Ghose, S. Krishna, K. S. Narang, and J. N. Răy, *Curr. Sci.* **4**, 158 (1935).

³⁶⁵ G. W. Cambridge, A. B. A. Jansen, and D. A. Jarman, *Nature (London)* **196**, 1217 (1962).

³⁶⁶ V. N. Plugar, T. T. Gorovits, N. Tulyaganov, and Ya. V. Rashkes, *Khim. Prir. Soedin.*, 250 (1977) [*CA* **87**, 111251 (1977)].

9-(2-Oxopropyl)tetrahydropyrrolo[2,1-*b*]quinazoline **190** was oxidized to the tetrahydropyrrolo[2,1-*b*]quinazolinone **95** with potassium permanganate in acetone.¹⁷³

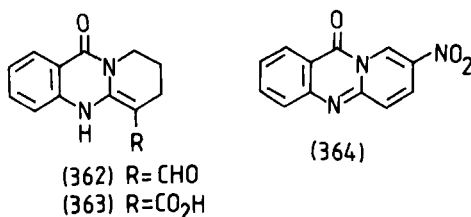
Oxidation of the dihydropyrido[2,1-*b*]quinazolinones **360** with chloranil afforded the pyrido[2,1-*b*]quinazolinones **361**.^{232,367}



6-Formyltetrahydropyrido[2,1-*b*]quinazolinone (**362**) was oxidized to the 6-carboxylic acid **363** with potassium permanganate in pyridine at ambient temperature.³⁶⁸

Oxidation of the hydroxytetrahydropyrrolo[2,1-*b*]quinazoline **184** with potassium permanganate in sulfuric acid gave the quinazolin(3*H*)-4-one,^{87,345} whereas oxidation in basic and neutral media yielded the 4-oxo-3*H*-quinazoline-3-acetic acid.^{85,133,142,145}

From a reaction mixture of anisessine (**193**) and potassium permanganate in acetone at 24°C, ethyl anthranilate was isolated.¹²⁴



With potassium permanganate under basic or neutral conditions,^{214,216,338} the pyrido[2,1-*b*]quinazolinone **286** and its 8-nitro derivative **364** yielded the quinazolin(3*H*)-4-one, while in acidic medium²⁵⁹ the product was the 2,4-dioxo-1,2,3,4-tetrahydroquinazoline.

Oxidation of azepine[2,1-*b*]quinazolinone **306** in acetic acid at 60°C with 90% hydrogen peroxide afforded *N*-(*o*-nitrobenzoyl)- ϵ -caprolactam (**305**).³³⁴

³⁶⁷ T. Yokoyama, K. Shibata, O. Fujii, and E. Iwamoto, Japan Kokai 76/42,725 [*CA* **85**, 48276 (1976)].

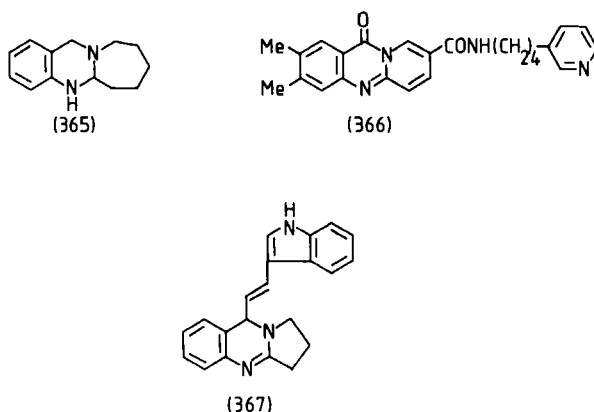
³⁶⁸ J. Kökösi, I. Hermecz, B. Podányi, Gy. Szász and Z. Mészáros, *J. Heterocycl. Chem.* **21**, 1301 (1984).

4. Quaternization, *N*-Alkylation, *N*-Dealkylation, *N*-Acylation, and *N*-Deacylation

The quaternization of vasicine (**184**), tricyclic compounds of types **205**, **211**, **244**, and **333**, and the decahydropyrido[2,1-*b*]quinazolinones **341** and **344** occurred on the nonbridgehead nitrogen atom,^{84,181,246,259,266,275,297,340,343,349,350,369} while that of the azepino[2,1-*b*]quinazolines **350** and **365** proceeded on the bridgehead nitrogen atom.^{328,339}

The quaternization of the pyrido[2,1-*b*]quinazolinone **366** with methyl iodide took place on the pyridine nitrogen atom.²³⁵

The alkylation of the hexahydropyrido[2,1-*b*]quinazolinone (**102**) with ω -aminoalkyl chloride in dimethylformamide in the presence of sodium hydride³⁷⁰ and the reaction of the perhydropyrido[2,1-*b*]quinazolinones **343** (*R* = H) and **346** (*R* = H) with methyl iodide in acetone in the presence of silver oxide^{349,350} led to products alkylated on the nonbridgehead nitrogen atom.



The indole nitrogen of 9-(3-indolylvinyl)pyrrolo[2,1-*a*]quinazoline (**367**) was methylated with methyl iodide in the presence of sodium hydride in dimethylformamide under a nitrogen atmosphere at room temperature.³³¹

The acylamino group of pyrrolo[2,1-*b*]quinazolinone was *N*-methylated with methyl iodide in the presence of sodium hydride.³⁵⁵

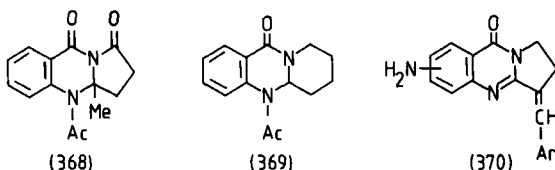
Debenzylation of 4-benzylhexahydropyrrolo[2,1-*b*]quinazolin-1,9-dione (**226**) by catalytic hydrogenation over palladium on carbon in acetic acid yielded the hexahydropyrrolo[2,1-*b*]quinazoline-1,9-dione **84**.³⁶ When the

³⁶⁹ S. V. Andrianova, K. Dil'manova, T. V. Kovtun, and A. V. Stetsenko, *Ukr. Khim. Zh. (Russ. Ed.)* **49**, 978 (1983) [*CA* **99**, 214134 (1983)].

³⁷⁰ J. Bernstein and E. R. Spitzmiller, U.S. Patent 3,271,396 [*CA* **66**, 10960 (1967)].

quaternary iodide **316** ($n = 2$) was heated in pyridine, it was demethylated to the azepino[2,1-*b*]quinazolinone **306**.¹⁸¹

Acylation of the hexahydropyrrolo[2,1-*b*]quinazoline-1,9-dione **84**³⁶ and the hexahydropyrido[2,1-*b*]quinazolinone **102**¹⁷⁹ with acetic anhydride in pyridine yielded the N-acetylated products **368** and **369**, respectively.

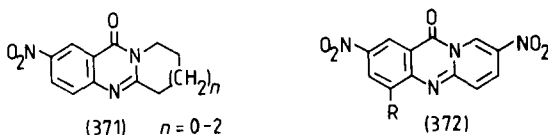


The amino group of the pyrrolo[2,1-*b*]quinazolines **195**, **205** ($R = NH_2$, $n = 0$), **356**, and **370** could be acylated with acid anhydrides^{95,183,210,344,357,358} and acid chlorides.³⁵⁵ The acetamido group of the pyrido[2,1-*b*]quinazolinones **211** ($R = NHAc$) was hydrolyzed to an amino group by the action of dilute sulfuric acid.²¹⁷

5. Electrophilic Substitution

Nitration of the tricyclic derivatives **99** with concentrated nitric acid in concentrated sulfuric acid at 0–25°C afforded the nitro derivatives **371**.^{183,343,356,371,372}

Binz and R  th²¹³ reported in 1931 that nitration of the pyrido[2,1-*b*]quinazolinone **286** with 30% nitric acid in concentrated sulfuric acid at 30°C gave the 2-nitropyrido[2,1-*b*]quinazoline **218**, whereas with 67% nitric acid in concentrated sulfuric acid at 50°C the 2,8-dinitro derivative **372** ($R = H$) was obtained. (The structures originally suggested for the products were not correct.)



Nitration of the 8-nitropyrido[2,1-*b*]quinazoline **364** with nitric acid in concentrated sulfuric acid led to the 2,8-dinitro derivative **372** ($R = H$) at

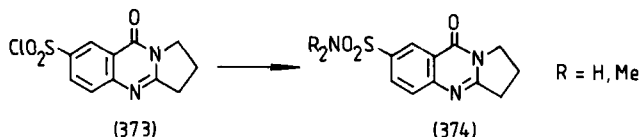
³⁷¹ E. Oripov, Kh. M. Shakhidoyatov, Ch. Sh. Kadyrov, and N. D. Abdullaev, *Khim. Geterotsikl. Soedin.*, 684 (1979) [*CA* **91**, 175290 (1979)].

³⁷² Kh. M. Shakhidoyatov, E. O. Oripov, L. M. Yun, M. Ya. Yamankulov, and Ch. Sh. Kadyrov, *Fungitsidy*, 66 (1980) [*CA* **94**, 192253 (1981)].

0–20°C, and to the 2,4,8-trinitrophenylido[2,1-*b*]quinazoline **372** ($R = \text{NO}_2$) at 40–60°C.²⁶³

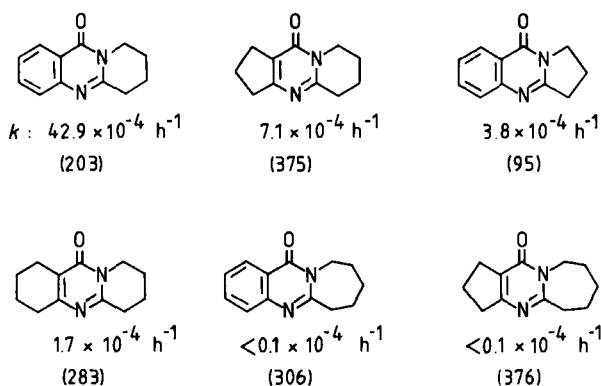
The pyrido[2,1-*b*]quinazolinone **286** and its 2,8-dinitro derivative **372** ($R = \text{H}$) were brominated with bromine in acetic acid, but the structures of the brominated products were not elucidated.^{213,259} Treatment of **286** with phosphorus pentachloride in phosphoryl chloride at 180–190°C yielded a trichlorinated product.²⁵⁹

The reaction of the tetrahydropyrrolo[2,1-*b*]quinazolinone **95** with chlorosulfonic acid at 0°C gave the chlorosulfonyl derivative **373**, which was then converted to the sulfonamides **374** by the action of amines.^{371,372}



6. Active Methylene Group Reactions and Some Subsequent Changes

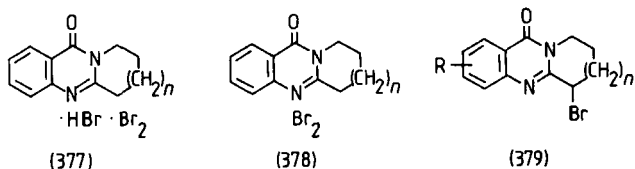
Tricyclic derivatives of types **205**, **248**, and **270** contain an active methylene group attached to the carbon atom of the imine moiety.^{373,374} To determine the relative reactivity of the active methylene group, deuteration experiments with deuterium oxide were carried out on the hydrochloride salts of **95**, **203**, **283**, **306**, **375**, and **376**. The results were evaluated means of ¹H-NMR spectroscopy.³⁷⁴ The deuteration rates k were:



³⁷³ A. D. Dunn, E. L. M. Guy, and K. I. Kinnear, *J. Heterocycl. Chem.* **20**, 779 (1983).

³⁷⁴ I. Hercmez, B. Podányi, and J. Kökösi, unpublished results.

The tricyclic derivatives **99** ($n = 0-2$) readily formed hydrobromide-bromine complexes on the addition of bromine in chloroform at ambient temperature.^{344,371,372} These complexes (**377**) underwent reversible conversion to the bromine complexes **378** on treatment with 5% sodium hydrogen carbonate.^{344,371,372}



Bromination of compounds of type **99** ($n = 0-2$) with *N*-bromosuccinimide in refluxing carbon tetrachloride in the presence of benzoyl peroxide led in general to the bromo derivatives **379**.^{175,182,344,371,372,375} If bromination was carried out with bromine in acetic acid, the dibromo compounds **380** were obtained.^{344,371,372,376,377}

Shakhidoyatov and co-workers^{372,375} obtained the 3-bromo-3-formyl-tetrahydropyrrolo[2,1-*b*]quinazolinone **382** when they treated the dimethyl-aminomethylene derivative **381** with bromine in refluxing chloroform.

The 3-chlorotetrahydropyrrolo[2,1-*b*]quinazoline **336** and its 9-oxo derivative **383** were prepared from vasicine (**184**), vasicinone (**185**), and vasicol (**191**) by the action of thionyl chloride,²⁵⁴ phosphoryl chloride,^{85,162} or a mixture of phosphoryl chloride and phosphorus pentachloride.³⁴⁵

The bromo substituent of **379** ($n = 0-3$) was exchanged for an acetoxy group by the action of sodium acetate in acetic acid at 130–140°C.^{175,182,378} The acetoxy group was then hydrolyzed to a hydroxy group with alkali.^{175,182,378} When the 3-bromotetrahydropyrrolo[2,1-*b*]quinazolinones **379** ($n = 0$) were heated with aromatic amines at 70°C, the 3-aminotetrahydropyrrolo[2,1-*b*]quinazolinones **384** were formed.¹⁷⁵

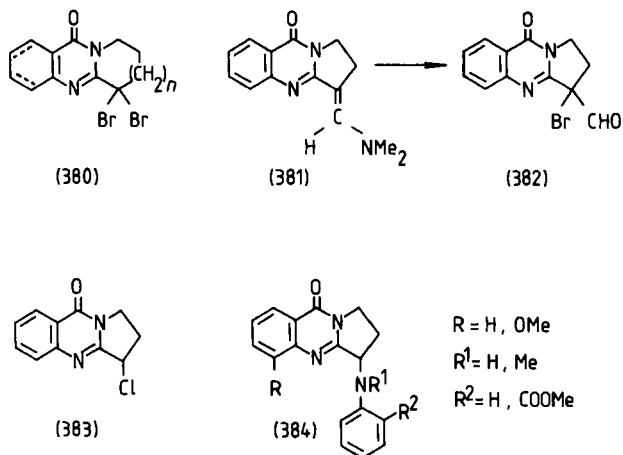
The tetrahydropyrrolo[2,1-*b*]quinazoline **124** and tricyclic compounds of type **205** ($n = 0, 1$) reacted with aromatic and heteroaromatic aldehydes to yield the condensation products **385** and **386**, respec-

³⁷⁵ E. Oripov, L. M. Yun, Kh. M. Shakhidoyatov, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 603 (1978) [*CA* **90**, 87388 (1979)].

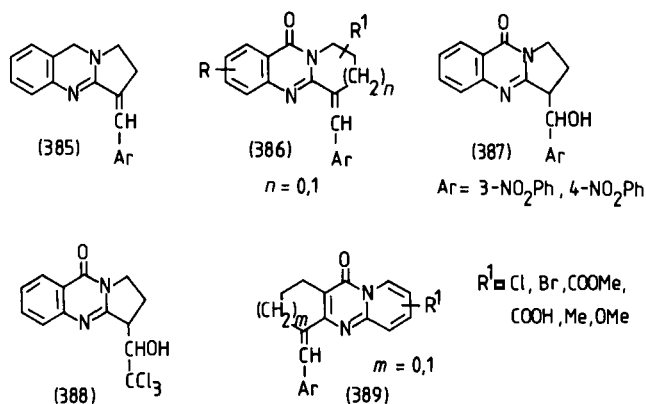
³⁷⁶ J. Kökösi, I. Hermecz, Gy. Szász, and Z. Mészáros, *Tetrahedron Lett.* **22**, 4816 (1981).

³⁷⁷ I. Hermecz, J. Kökösi, L. Vasvári-Debreczy, Á. Horváth, B. Podányi, Gy. Szász, and Z. Mészáros, *Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. [Proc.]*, 1st, 1981, Vol. 3(2), p. 69 (1981) [*CA* **97**, 127863 (1982)].

³⁷⁸ V. N. Plugar, Ya V. Rashkes, and Kh. M. Shakhidoyatov, *Khim. Prir. Soedin.*, 180 (1979) [*CA* **92**, 76758 (1980)].



tively.^{124,183,210,254,321,355,357,372,379-381} Reactions were carried out in the melt,^{124,183,254,321,357,372,379} in refluxing xylene,^{380,381} and in refluxing methanol in the presence of sodium methoxide.^{210,355} Shakhidoyatov *et al.*^{372,379} succeeded in preparing the condensation products of type **387** by treating **95** with *m*- and *p*-nitrobenzaldehydes and applying shorter reaction periods. With trichloroacetaldehyde the condensation product **388** was obtained.³⁷² 2-Aminobenzaldehyde,¹⁸³ aliphatic aldehydes³⁷⁹ (e.g., nonyl aldehyde and crotonaldehyde), and ketones^{372,379} (cyclopentanone, cyclohexanone, and benzophenone) did not react.



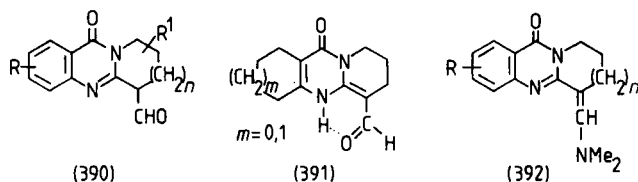
³⁷⁹ Kh. M. Shakhidoyatov, M. Ya. Yamankulov, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 552 (1977) [*CA* **88**, 7166 (1978)].

³⁸⁰ V. N. Gupta, M. P. Jain, C. K. Atal, and M. Bhardawaj, *Indian J. Chem., Sect. B* **21B**, 74 (1982).

³⁸¹ V. K. Sharma and M. P. Jain, *Indian J. Chem. Sect. B* **21B**, 75 (1982).

The reaction of the tricyclic compounds **244** ($R = H$, $n = 0, 1$) with aromatic aldehydes in methanol in the presence of sodium methoxide afforded the condensation products **389**.²⁶⁸

Vilsmeier-Haack formylation of the tricyclic compounds of types **205** and **333** with dimethylformamide-phosphoryl chloride reagent gave the formylated products **390** and **391**.^{217,371,372,375,382,383} (For the structures of **390** and **391**, see Section V.D.) From reaction mixtures of the five- and six-membered homologs **205** ($n = 0, 1$) the intermediate dimethylaminomethylene derivatives **392** ($n = 0, 1$) could also be isolated. These were then converted to the formyl derivatives **390** ($n = 0, 1$). The seven-membered homolog **306** did not react, though its nitro derivative **371** ($n = 2$) did.^{372,383}

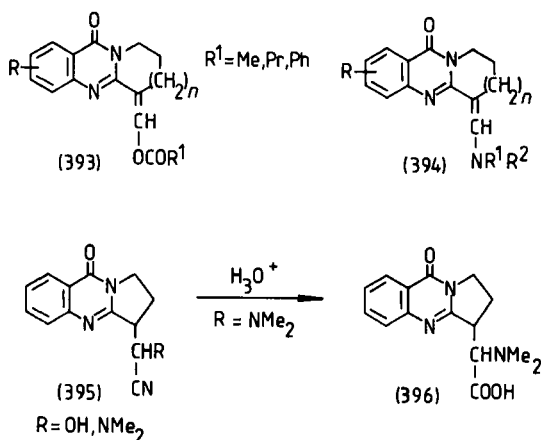


The 3-(dimethylaminomethylene)pyrrolo[2,1-*b*]quinazolinone **381** was transformed with sodium acetate to the acetoxymethylene derivative **393** ($R = H$, $R^1 = Me$, $n = 0$), which was deacetylated by the Zemplén method to the formyl derivative **390** ($R = R^1 = H$, $n = 0$).³⁸³ The acyloxymethylene derivatives **393** were obtained from other dimethylaminomethylene and formyl derivatives, (**390** and **392**, $n = 0, 1$), by reaction with acid anhydrides.^{372,375}

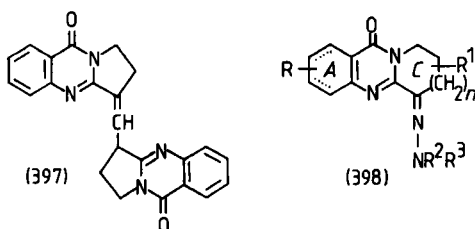
The five-membered homolog of **390** ($R = R^1 = H$, $n = 0$) gave the dimethylaminomethylene derivative **381** upon treatment with dimethylamine.^{371,382} The formyl compounds **390** ($n = 0, 1$) and the dimethylaminomethylene derivatives **392** were transformed by amines, hydrazines, and hydroxylamine into the corresponding 3-aminomethylene derivatives of type **394**.^{367,370} The dimethylaminomethylene compound **381** and the formyl derivative **390** ($R = R^1 = H$, $n = 0$) afforded cyano derivatives **395** on treatment with acetone cyanohydrin.^{372,375} Compound **395** ($R = NMe_2$) was hydrolyzed to the acetic acid derivative **396** in concentrated hydrochloric acid.^{372,375} Treatment of the (dimethylaminomethylene) pyrrolo[2,1-*b*]quinazolinone **381** with formic acid furnished the bis derivative **397**.^{372,375} The formyl and dimethylaminomethylene groups of compounds

³⁸² Kh. M. Shakhidoyatov, E. Oripov, A. Iriobaev, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 825 (1976) [*CA* **86**, 106520 (1977)].

³⁸³ Á. Horváth, I. Hermecz, M. Pongor-Csákvári, Z. Mészáros, J. Kökösi, G. Tóth, and Á. Szöllösy, *J. Heterocycl. Chem.* **21**, 219 (1984).



of types **390** and **392** could be eliminated by alkaline or acidic hydrolysis to give the starting tricyclic derivatives **205**.^{371,372,375}



6-Arylhydrazonopyrido[2,1-*b*]quinazolinones and their homologs in rings A and C (**398**) were prepared from tetra- and octahydro-pyrido[2,1-*b*]quinazolinones and their homologs (**205** and **333**) or from 6-(carboxyl-6-formyl-, and 6-dimethylaminomethylene)pyrido[2,1-*b*]quinazolinones and their homologs (**363** and **390–392**) by diazo coupling with aryldiazonium salts.^{217,368,384,385} The hydrazono derivatives **398** can also be prepared from the bromo- and dibromo-substituted tricyclic compounds **379** and **380**^{217,368,384} by treating them with hydrazines.

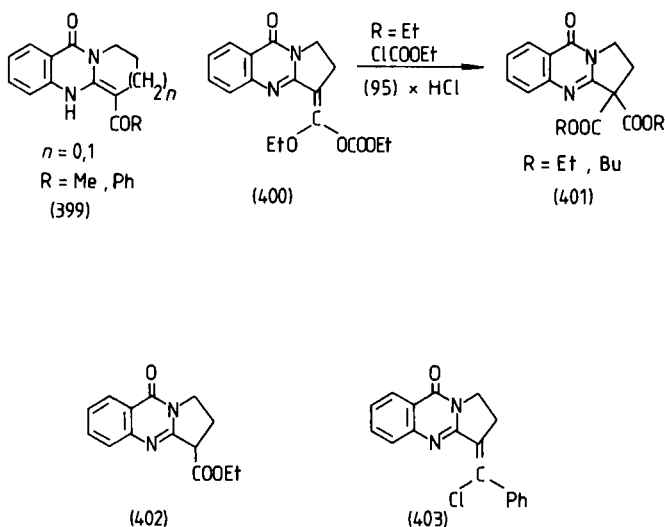
The quaternary salts **316** ($n = 0, 1$) were acylated to **399** during heating in acetic anhydride in the presence of sodium acetate and potassium acetate and by reaction with benzoyl chloride in pyridine at $100^\circ C$.^{181,201} Further acylation reactions leading to ring transformation are discussed in Section V,C,7.

³⁸⁴ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 889,339 [CA 96, 85577 (1982)].

³⁸⁵ I. Hermecz, Á. Horváth, Z. Mészáros, Gy. Szász, T. Breining, and L. Vasvári-Debreczy, U. S. Patent 4,395,549 [CA 99, 176132 (1983)].

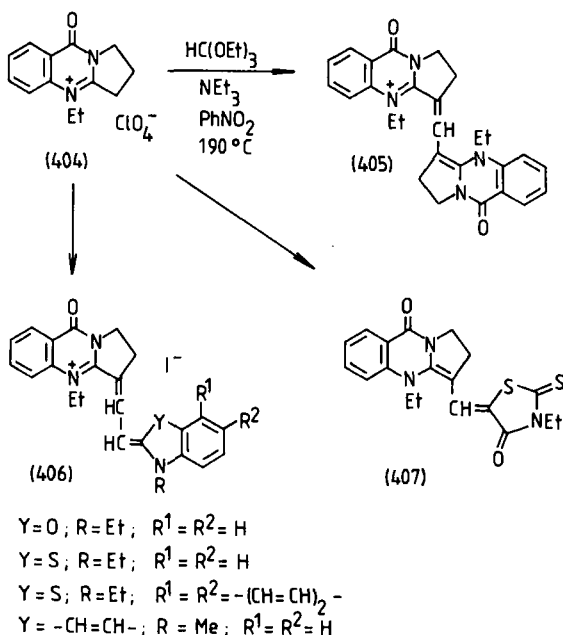
Dunn *et al.*³⁷³ investigated the reactions of the tetrahydropyrrolo[2,1-*b*]quinazolinone **95** with alkyl chloroformates and with benzoyl chloride. When the pyrrolo[2,1-*b*]quinazolinone **95** was heated in alkyl chloroformates, the product was dependent on the length of the reaction period. Reaction for 8–10 hr favored the formation of compound **400**, while longer reaction times afforded the dialkyl pyrrolo[2,1-*b*]quinazoline-3,3-dicarboxylates **401** and 2-ethoxy-4*H*-3,1-benzoxazin-4-one. Conversion of compound **40** to the diester **401** (R = Et) was easily accomplished by heating it with ethyl chloroformate in the presence of the hydrochloride salt of **95**. Ethyl pyrrolo[2,1-*b*]quinazoline-3-carboxylate (**402**) was obtained when the diethyl pyrrolo[2,1-*b*]quinazoline-3,3-dicarboxylate **401** (R = Et) was allowed to stand overnight at ambient temperature in ethanol presaturated with dry gaseous ammonia.

When the tetrahydropyrrolo[2,1-*b*]quinazolinone **95** or its hydrochloride salt was heated in benzoyl chloride, the product of the reaction was the α -chlorobenzylidine derivative **403**.³⁷³



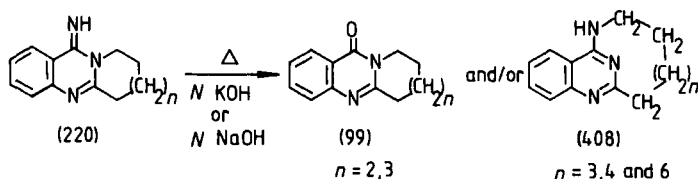
The quaternary pyrrolo[2,1-*b*]quinazolinium salt **404** yielded the bis compound **405** with triethyl orthoformate in nitrobenzene in the presence of triethylamine at 190°C.³⁶⁹ The active methylene group of **404** readily reacted with the 2-[(2-acetanilido)vinyl] derivatives of 3-alkylbenzoxazolium, benzthiazolium, naphtho[2,1-*d*]thiazolium, and 1-methylquinazolium iodides in acetic anhydride at 100°C in the presence of triethylamine to give the cyanines **406**. Reaction of **404** with 3-ethyl-5-(acetanilidomethylene)rhodanine in refluxing pyridine in the presence of triethylamine af-

forded the merocyanine **407**.³⁶⁹ The methylene group of **404** was also condensed with *p*-dimethylaminobenzaldehyde.³⁶⁹

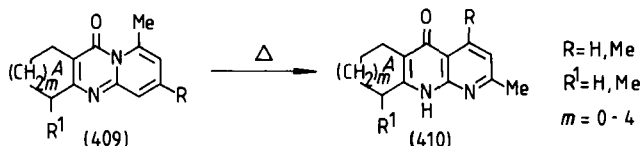


7. Ring Transformation

Brown and Ienage²⁴⁵ studied the Dimroth rearrangement of the tricyclic imines **220**. In aqueous alkali the seven-membered homolog **220** ($n = 2$) gave only one product, the corresponding azepino[2,1-*b*]quinazolin-12-one **99** ($n = 2$), because the chain of five methylene groups was too short to permit the existence of a rearranged isomer of type **408** without considerable strain. The next higher homologous imine **220** ($n = 3$) afforded a mixture of the oxo analog **99** ($n = 3$) and the β -bridged isomer **408** ($n = 3$). The nine- and eleven-membered homologs **220** ($n = 4$ and 6), with adequately long chains, gave only the respective rearranged isomers **408** ($n = 4$ and 6).



Bernáth *et al.*²⁶⁶ reported that the tricyclic nitrogen bridgehead compounds **409** were transformed in good yields into the isomeric 1,8-naphthyridine derivatives **410** by the action of heat, independently of the size of ring A. Ring transformation is facilitated owing to the nearly coplanar disposition of the carbonyl and methyl groups. The strain caused by the interaction of these groups is relieved when the C—N bond cleaves.



Kametani *et al.*^{313,386} found that 3-(*o*-nitrobenzal)tetrahydropyrrolo[2,1-*b*]quinazolinone (**355**) with 2 molar equivalents of triethyl phosphite at 170°C under a nitrogen atmosphere for 20 hr gave 3-(*o*-ethylamino-benzal)tetrahydropyrrolo[2,1-*b*]quinazolinone (**356**) and pseudorutecarpine (**411**) in 43 and 6% yields, respectively.

Fischer indolization of the arylhydrazono derivatives **412** in polyphosphoric acid or in the presence of anhydrous zinc chloride at 160–180°C afforded pentacyclic indole derivatives.^{376,377,385,387–389} Kökösi and co-workers started from tricyclic arylhydrazones of type **412** and synthesized various products in high yields, including the alkaloid rutecarpine (**413**, $R = R^1 = R^2 = \text{H}$, $n = 1$, ring E = aromatic),³⁷¹ its homologs in ring C (**413**, $n = 0, 2$),^{385,387,388} and derivatives with saturated five- and six-membered ring E.³⁸⁹

Shemyakin and co-workers^{181,201} obtained the pyrone derivatives **418** when the quaternary salts **316** were treated with excess acetic anhydride in the presence of potassium carbonate or sodium acetate at reflux temperature for 8 hr. Under such drastic conditions the primarily formed *C*-acety compounds **414** underwent further transformation to the pyrone derivatives **418** via intermediates **415–417**. The reactivity of the quaternary salts **316** toward this conversion increased in the sequence $n = 0 < n = 1 < n = 2$.

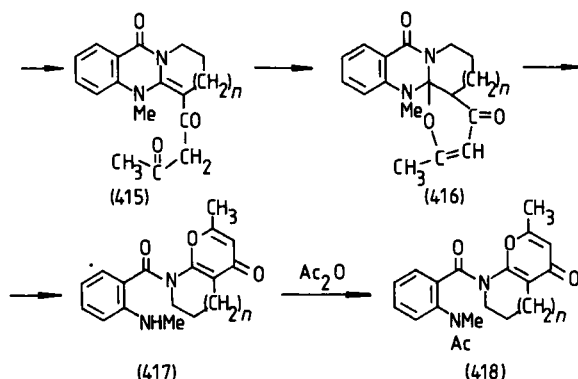
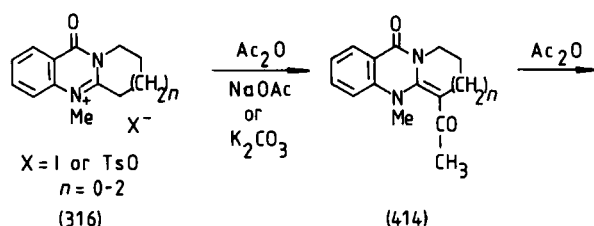
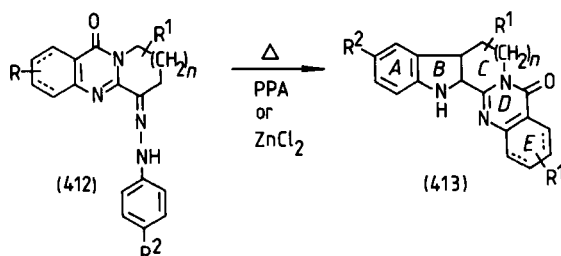
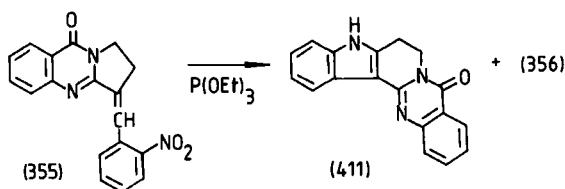
When a reaction time of 20 min had elapsed, the *C*-acylated compounds **414** ($n = 0, 1$) could be isolated, which were then converted in a separate step to the pyrane derivatives **418** ($n = 0, 1$).¹⁸¹

³⁸⁶ T. Kametani, Japan Kokai 74/85,100 [CA 82, 4452 (1975)].

³⁸⁷ J. Kökösi, I. Hermecz, Z. Mészáros, S. Virág, L. Vasvári-Debreczy, Gy. Szász, Á. Horváth, T. Breining, T. Szűts, and Gy. Sebestyén, Fr. Demande 2,485,533 [CA 97, 24059 (1982)]; CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 889,337 [CA 96, 104584 (1982)].

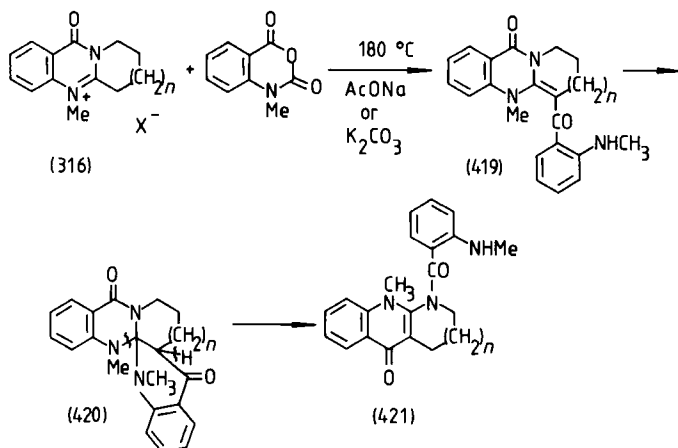
³⁸⁸ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 889,338 [CA 96, 104585 (1982)].

³⁸⁹ J. Kökösi, I. Hermecz, Gy. Szász, and Z. Mészáros unpublished results.



When the quaternary salts **316** were treated with *N*-methylisatoic anhydride in the presence of bases, the *N*-anthraniloyl compounds **421** were obtained.^{201,202} The initially formed *C*-anthraniloyl derivatives **419** underwent transformation to *N*-anthraniloyl derivatives **421** via the orthoamides **420**. The isomerization of the orthoamides **420** to *N*-anthraniloyl derivatives

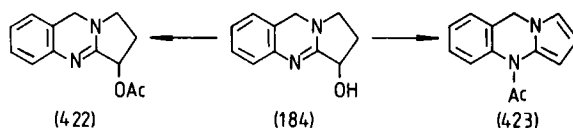
appears to proceed by thermal syn-1,2-elimination without being accelerated substantially by acids or bases.



The orthoamide **420** ($n = 0$) could also be isolated from the mother liquor of the five-membered homolog **421** ($n = 0$).^{201,202}

8. Miscellaneous Reactions

The aliphatic^{98,162,341,365} and/or aromatic^{98,182} hydroxy group of the pyrrolo[2,1-*b*]quinazolines **205** ($n = 0$, $R = 7\text{-OH}$, $R^1 = \text{H}$ or OH), **184**, and **185** was acylated with acetic anhydride.

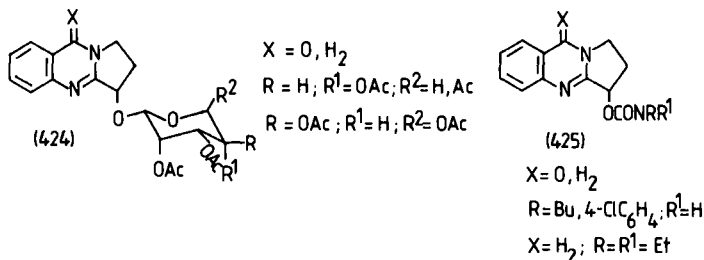


In a reaction with acetic anhydride at 100 °C for 1 hr vasicine (**184**) was reported to give the *O*-acetyl derivative **422**, while in 2.5 hr at 100 °C the product was the *N*-acetyl derivative **423**.³⁴¹ The latter was deacetylated by treatment with 2% potassium hydroxide and the resultant 4,9-dihydropyrrolo[2,1-*b*]quinazoline was acetylated back with acetic anhydride.³⁴¹

The hydroxy group of the pyrrolo[2,1-*b*]quinazoline **331** was acylated with benzoyl chloride in pyridine.³⁴³

The 3-acetoxy group of the pyrrolo[2,1-*b*]quinazolines **205** ($n = 0$, $R^1 = 3\text{-OAc}$) and **263** ($n = 0$, $R = \text{H}$, $R^1 = 3\text{-OAc}$, $X = \text{H}_2$) was converted to a hydroxy group by alkaline hydrolysis.^{341,365}

From the pyrrolo[2,1-*b*]quinazolines **184** and **185** the glycosides **424** were prepared by reaction with bromo sugars,³⁹⁰ and the carbamates **425** ($R^1 = H$) with isocyanates.^{193,391} The carbamate **425** ($X = H_2$, $R = R^1 = Me$) was also produced from vasicine (**184**) on treatment successively with phosgene and dimethylamine.¹⁹³



The hydroxy group of the 3-hydroxyl-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline **184** was esterified with C_3-C_{18} carboxylic acids in the presence of dicyclohexyl carbodiimide in chloroform.³⁹²

Hydration of vasicine (**184**) to the dihydroxypyrroloquinazoline **191** proceeded in aqueous solution in a sealed tube at 140–150°C during 16 hr.¹⁶² Methylation of this produce (**191**) with trimethylanilinium hydroxide resulted in a mixture of the pyrrolo[2,1-*b*]quinazolines **426** and **427**, which were then acetylated with acetic anhydride.¹⁶²

The passage of gaseous hydrogen chloride into a dry methanolic solution of **191** resulted in the formation of vasicine hydrochloride (**184**·HCl). Treatment of **191** with phosphoryl chloride in pyridine afforded the 3-chloropyrrolo[2,1-*b*]quinazoline **336**.¹⁶²

The aromatic hydroxy group of vasicinolone (**188**) was methylated with trimethylanilinium hydroxide,¹⁷² and that of the pyrido[2,1-*b*]quinazoline **211** ($R = OH$) was ethylated with ethyl iodide in dimethylformamide in the presence of potassium carbonate.²²³

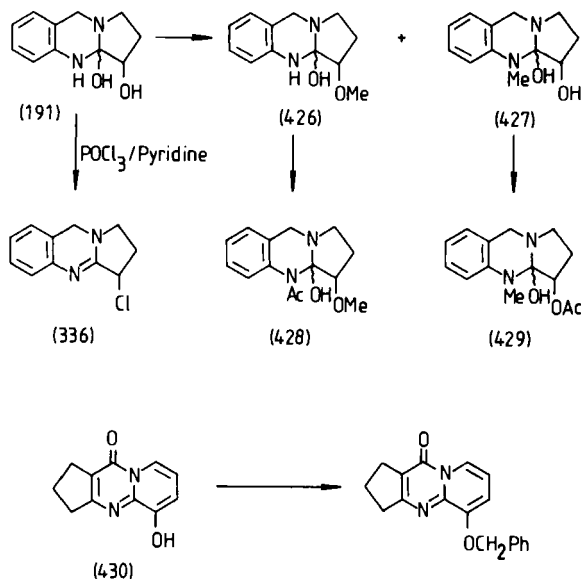
The hydroxy group of the cyclopenta[*d*]pyrido[1,2-*a*]pyrimidine (**430**) was alkylated with benzyl bromide in dimethylformamide in the presence of sodium hydride and copper bronze,²⁶¹ in boiling xylene in the presence of copper bronze,²⁶¹ or in boiling 2-butanone in the presence of potassium bicarbonate.²⁶²

The alkoxy group of the pyrrolo[2,1-*b*]quinazolines **205** and **325** ($n = 0$, $R = OMe$) and of the pyrido[2,1-*b*]quinazolinones **211** ($R = OMe$) and **389**

³⁹⁰ S. John, K. Seifert, and S. Haertling, *Pharmazie* **34**, 197 (1979).

³⁹¹ Kh. M. Shakhidoyatov, F. Kiyamitdinova, and Ch. Sh. Kadyrov, *Khim. Prir. Soedin.*, 765 (1975) [*CA* **84**, 150822 (1976)].

³⁹² V. N. Gupta, R. Manavalan, and C. K. Atal, *Indian J. Pharm. Sci.* **44**, 54 (1982).



($m = 1$, $\text{Ar} = 3\text{-EtOPh}$) was converted to a hydroxy group by reaction with 48% hydrobromic acid,^{182,193,194} hydrogen bromide in acetic acid,¹⁷¹ a 1:1 mixture of concentrated hydrochloric acid and acetic acid,²⁶⁸ or in melted pyridine hydrochloride at 220°C for 2 hr.²²³

The oxo group of **205** ($n = 1$ and 3) was transformed into a thioxo group by phosphorus pentasulfide in refluxing xylene³⁴⁷ or pyridine.⁵⁷

The carboxylic group attached to a ring or a side-chain carbon atom in the tricyclic compounds **211**, **244**, **386**, and **389** was esterified by known procedures.^{221,224,235,238,246,267,268,355,383}

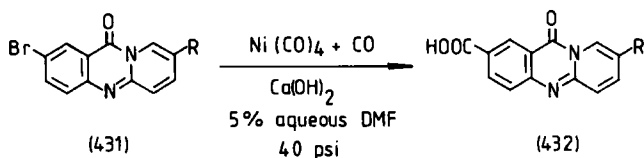
The pyrido[2,1-*b*]quinazolinone amyl ester **211** ($\text{R}^1 = \text{COOAm}$) was also obtained by transesterification.²²⁴

The carboxyl groups in the tricyclic compounds **211** (R or $\text{R}^1 = \text{COOH}$), **386** ($\text{R}^1 = \text{COOH}$) were transformed with thionyl chloride into chlorocarbonyl groups,^{210,217,224,235,237,238,268} which were converted by amines to the amides,^{210,217,224,235,237,238} with alcohols to the esters,^{210,217,224,268} and with hydroxylamine to the hydroxamic acids.²¹⁷

Carboxamides of the tricyclic compounds **244** ($n = 1$, $\text{R}^1 = \text{CONH}_2$) and **389** ($m = 1$, $\text{R}^1 = \text{CONH}_2$) were obtained from the appropriate esters or from carboxylic acids with ammonia, via mixed anhydrides.^{267,268} *N*-Substituted carboxamides of the pyrido[1,2-*a*]quinazolinones **211** ($\text{R}^1 = \text{CONHR}^2$) were prepared directly from the corresponding acids with amines in the presence of diphenylphosphoryl azide and triethylamine in dimethylformamide at -5°C ^{224,235} or were obtained from esters with amines.²³⁵

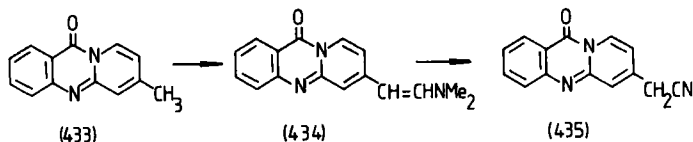
Carboxylic acids of the tricyclic compounds **211**, **244**, **386**, and **389** were obtained by hydrolysis of the appropriate esters,^{231,267,268,355} nitriles^{221,230,231} and amides.^{236,267}

The carboxylic acids **432** were prepared from the bromopyrido[2,1-*b*]-quinazolinones **431** by the modified Cassar method, with carbon monoxide in 5% aqueous dimethylformamide under 40 psi pressure, or by the use of an equimolar amount of nickel carbonyl in the presence of calcium hydroxide.^{220,221}



The methyl group of the pyrido[2,1-*b*]quinazolinones **211** (R or $R^1 = \text{Me}$) was brominated with *N*-bromosuccinimide in the presence of azobisisobutyronitrile to give bromomethyl derivatives.²²⁹⁻²³¹ The bromomethyl group was converted to a cyanomethyl group by treatment with alkali-metal cyanide,^{230,231}

The cyanomethyl group was also prepared from the dimethylaminovinyl group, formed from the methyl group with bis(dimethylamino)-*tert*-butoxymethane, by treatment with hydroxylamin-*O*-sulfonic acid in water at room temperature (**433** \rightarrow **434** \rightarrow **435**).^{230,393}



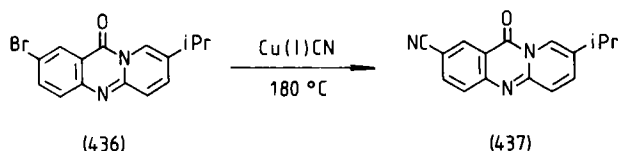
The cyanomethyl-substituted pyrido[2,1-*b*]quinazolinones **211** ($R = \text{CH}_2\text{CN}$) can be transformed by chain elongation into the propionic acid and propionic acid ester derivatives. Reactions were effected by heating the cyanomethyl derivatives for 2 hr in diethyl carbonate in the presence of sodium hydride, followed by evaporation and treatment with methyl iodide and sodium hydride in dimethylformamide at 0°C , and finally by stirring of the evaporated oily residue in a mixture of isopropanol and concd. sodium hydroxide to obtain the acids,²³⁰ and in 0.5 *N* aqueous acetic acid to obtain the esters.²³¹

The carboxamide group in the tricyclic derivatives **211** (R or $R^1 = \text{CONH}_2$), **386** ($R = \text{CONH}_2$), and **389** ($R^1 = \text{CONH}_2$) was dehydrated to a

³⁹³ H. Biere and R. Russe, *Tetrahedron Lett.*, 1361 (1979).

cyano group by thionyl chloride in dimethylformamide^{217,237} or by heating in the presence of *p*-toluenesulfonyl chloride in a mixture of pyridine and dimethylformamide.^{210,225–227,236}

The cyano group was converted to a 5-tetrazolyl group as a result of treatment with sodium azide in dimethylformamide at 90–115°C for 10–15 hr in the presence of ammonium chloride.^{217,226,227,235–237}

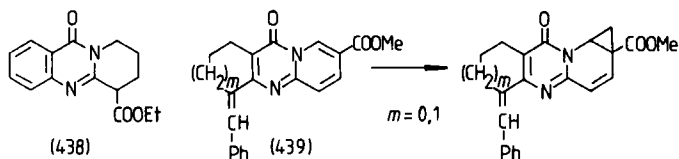


The 2-cyanopyrido[2,1-*b*]quinazolinone **437** was prepared from the 2-bromo derivative **436** with cuprous chloride in 1-methyl-2-pyrrolidinone at 180°C.²²¹

The benzoyloxymethyl group of the pyrido[2,1-*b*]quinazolinones **211** ($R^1 = \text{PhCOOCH}_2$) was hydrolyzed to a hydroxymethyl group in a mixture of concentrated hydrochloric acid and ethanol under reflux conditions.²³⁸

The acetyl group of the pyrido[2,1-*b*]quinazolinone **211** $R^1 = \text{COMe}$ was converted to a 1-(methoxyimino)ethyl group by reaction with methoxyamine hydrochloride in pyridine at room temperature for 3 days.²²⁰

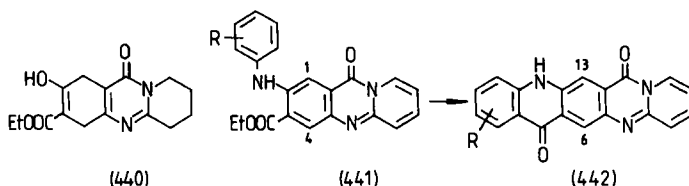
11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid was decarboxylated to the pyrido[2,1-*b*]quinazolinone **286**.²¹¹ Ethyl tetrahydro-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylate (**438**) was hydrolyzed and decarboxylated at 170–180°C to give the tetrahydropyrido[2,1-*b*]quinazolinone **203**.²⁰⁹



The tricyclic esters **439** were converted to the tetracyclic compounds by treatment with trimethylsulfoxonium iodide in dimethyl sulfoxide in the presence of sodium hydride.²⁶⁸

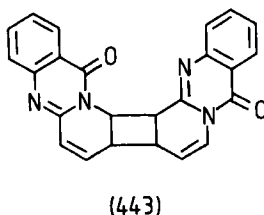
The 2-amino and 2-hydroxy groups of the dihydropyrido[2,1-*b*]quinazolinones **360** and **440** were converted to a 2-(arylamino) group by treatment with anilines in refluxing acetic acid for 2.5 hr under a nitrogen atmosphere.^{394,395} The pyrido[2,1-*b*]quinazolinones **441** and the 1,4-dihydro de-

rivatives were cyclized to the pentacyclic compounds **442** and its 6,13-dihydro derivative by heating in polyphosphoric acid.^{394,395}



The red pigment nordine (**201**) can take up two molecules of bromine.¹⁷⁶

Ultraviolet irradiation of the pyrido[2,1-*b*]quinazolinone **286** under a nitrogen atmosphere generated a compound $[C_{12}H_8N_2O]_n$, which, on being heated to 230–235°C or by the action of acid, yielded cyclobuta-[2,1-*h*;3,4-*j*]bis(pyrido[2,1-*b*]quinazoline)-5,16-dione (**443**).^{260,396} The structure of **443** was determined by X-ray.²⁶⁰ The four-membered ring of **443** is thermally labile and underwent [2 + 2] cyclofragmentation to give quantitative regeneration of the pyrido[2,1-*b*]quinazolinone **286**.²⁶⁰



D. PHYSICOCHEMICAL PROPERTIES

The following physicochemical data are available.

For the pyrrolo[2,1-*b*]quinazolines: UV,^{95,98,121,124,160,173,174,181,185,196,329,340,342,360}IR,^{92,98,105,121,124,173,174,181,185,196,201,312,327,340,357,373,397} ¹H-NMR,^{42,95,98,121,124,162,175,181,182,185,193,196,199,205,210,247,248,252,256,295,306,312,326,327,329,340,355,356,357,373,398} ¹³C-NMR,^{183,185,295,373} and mass spectral^{195,124,181,185,366,378,398–402} data.

³⁹⁴ Y. Yokoyama, *Nippon Kagaku Kaishi*, 398 (1979) [CA 91, 58676 (1979)].

³⁹⁵ Y. Yokoyama, *Bull. Chem. Soc. Jpn.* **56**, 1775 (1983).

³⁹⁶ L. D. Rodes, R. F. Pellon, N. M. Yur'eva, S. S. Trach, Yu. N. Luzikov, and M. V. Proskurina, *Rev. CENIC, Cienc. Fis.* **11**, 129 (1980) [CA 95, 195048 (1981)].

³⁹⁷ J. Fabian, M. Legrand, and P. Poirier, *Bull. Soc. Chim. Fr.*, 1499 (1956).

³⁹⁸ V. N. Plugar, N. D. Abdullaev, Ya. V. Rashkes, M. R. Yagudaev, and N. Tulyoganov, *Khim. Prir. Soedin.*, 758 (1983) [CA 100, 150574 (1984)].

For the pyrido[2,1-*b*]quinazolines: UV,^{169,181,229,232,266,267,271,275,276,376,403-405} fluorescence,²²⁹ IR,^{169,181,201,204,229,240,266,267,270,276,327,328,404} ¹H-NMR,^{42,179,187,206,229,247,248,268,271,275,276,295,327,328,349,350,376,405-408} ¹³C-NMR,^{187,295,407,408} and mass spectral^{169,179,229,378,401} data.

For the azepino[2,1-*b*]quinazolines: IR,^{181,201,327,328} ¹H-NMR,^{199,247,248,258,326-328,334,339} and mass spectral^{203,378,401} data.

For cyclopenta[*d*]pyrido[1,2-*a*]pyrimidines: UV,^{267,276} IR,^{261,267,276} and ¹H-NMR^{261,266,268,275} data.

For tricyclic derivatives of types **244** and **33** (*m* = 0-3): UV²⁶⁶ and IR²⁶⁶ data.

The structure and the absolute configuration of (-)-vasicine (**184**) were determined by X-ray crystallography⁴⁰⁹: (-)-vasicine has a 3*R* configuration, and the pyrrolidine ring displays an envelope conformation.

The chromatographic (TLC,^{118,164,410,411} GC,¹¹⁸ and HPLC¹²²) and polarographic³⁴⁶ behavior and mass spectral properties^{95,399,400,402} of some pyrolo[2,1-*b*]quinazoline alkaloids were investigated. A procedure for the rapid qualitative identification of vasicine (**184**) by means of capillary luminescence was developed.⁴¹²

Conformational analyses of hydrogenated pyrido[2,1-*b*]quinazolin-11-ones were carried out by ¹H- and ¹³C-NMR spectroscopy.^{187,349,350,405-408}

In the hexahydropyrido[2,1-*b*]quinazolinone **102** the proton 9-H_{eq} is al-

³⁹⁹ A. K. Bhatnagar and S. P. Popli, *Indian J. Chem.* **4**, 291 (1966).

⁴⁰⁰ Ya. V. Rashkes, M. V. Telezhenetskaya, V. N. Plugar, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 378 (1977) [*CA* **88**, 7152 (1978)].

⁴⁰¹ V. N. Plugar, Ya. V. Rashkes, and Kh. M. Shakhidoyatov, *Khim. Prir. Soedin.*, 414 (1978) [*CA* **89**, 128695 (1978)].

⁴⁰² V. N. Plugar, Ya. V. Rashkes, A. Karimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 68 (1983) [*CA* **98**, 197454 (1983)].

⁴⁰³ S. Carboni and M. Pardi, *Ann. Chim. (Rome)* **49**, 1228 (1959).

⁴⁰⁴ W. Leimagruber, A. D. Batcho, and F. Schenker, *J. Am. Chem. Soc.* **87**, 5793 (1965).

⁴⁰⁵ C. C. J. Culvenor, *Tetrahedron Lett.*, 1091 (1966).

⁴⁰⁶ H. Paulsen and K. Todt, *Chem. Ber.* **100**, 3385 (1967).

⁴⁰⁷ G. Tóth, F. Fülöp, G. Bernáth, K. Simon, I. Hermecz, and Z. Mészáros, *J. C. S. Perkin II*, 237 (1983).

⁴⁰⁸ G. Tóth, F. Fülöp, G. Bernáth, K. Simon, I. Hermecz, and Z. Mészáros, *Magy. Kem. Foly.* **89**, 369 (1983) [*CA* **100**, 5418 (1984)].

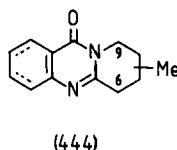
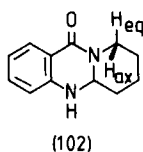
⁴⁰⁹ K. Szulzewoky, E. Höhne, S. Johnne, and D. Gröger, *J. Prakt. Chem.* **318**, 463 (1976).

⁴¹⁰ E. K. Dobronravova, A. Kh. Sattarova, and T. T. Shakirov, *Khim. Prir. Soedin.*, 127 (1983) [*CA* **96**, 223354 (1982)].

⁴¹¹ D. Gröger, *Pharmazie* **23**, 210 (1968).

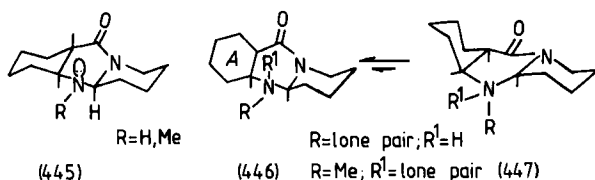
⁴¹² V. A. Shevelev, B. A. Krivut, and E. Ya. Kiseleva, *Aptechn. Delo* **14**, 56 (1965) [*CA* **64**, 4866f (1966)].

most coplanar with the carbonyl group, and its signal therefore appears at lower field (~ 4.6 ppm) than that of the proton 9-H_{ax} (~ 2.7 ppm).^{405,406}



As concerns the methyl-substituted tetra- and octahydropyrido[2,1-*b*]-quinazolinones **444**, the 7- and 8-methyl derivatives exist mainly in the conformation containing the methyl group in the quasiequatorial position.¹⁸⁷ For the 9-methyl derivatives the conformation containing the methyl group in the quasixial position predominates, which is a consequence of the allylic strain arising between the methyl and the carbonyl groups. The 6-methyl derivatives exist as mixtures of two conformers containing the methyl group in either the quasixial or the quasiequatorial position.¹⁸⁷

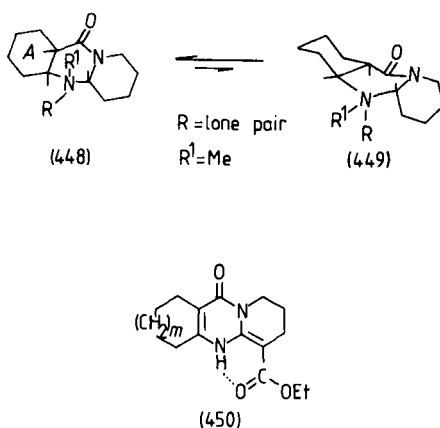
Tóth *et al.*^{349,350,407,408} established the conformations of three diastereomers of the dodecahydropyrido[2,1-*b*]quinazolin-11-ones **343**, **346**, and **347** ($R = H$ or Me). In the diastereomers **343**, characterized at positions C-4a, C-11a, and C-5a by relative configurations α, β, α , the predominant conformation is **445**, which contains 4a-H and the lone-pair electrons of N-5 in the antiperiplanar disposition. In the α, α, α diastereoisomers **346** the conformational equilibrium is shifted toward conformer **446**, in which N-5 is axial with respect to ring A, while the equatorial position is preferred for the *N*-methyl group and the axial position for the N-H proton.



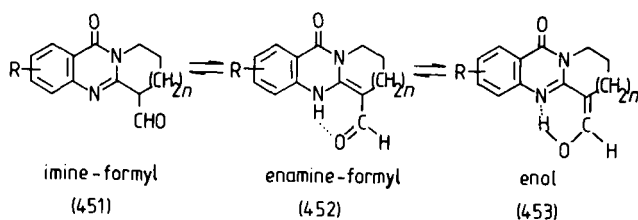
In the α, α, β diastereomers **347** the conformational equilibrium is shifted toward conformer **448**, in which the carbonyl group is axial with respect to ring A. In the methyl derivatives **347** ($R = Me$) the methyl group occupies the axial position.

In the solid state, the conformations of **343** ($R = H$) and **346** ($R = H$) are similar to those found in solution, but the hydrogen atom attached to N-5 always occupies the axial position.^{349,350}

The ester derivatives **450** ($m = 0, 1$) exist predominantly as enamine tautomers.²⁷⁶

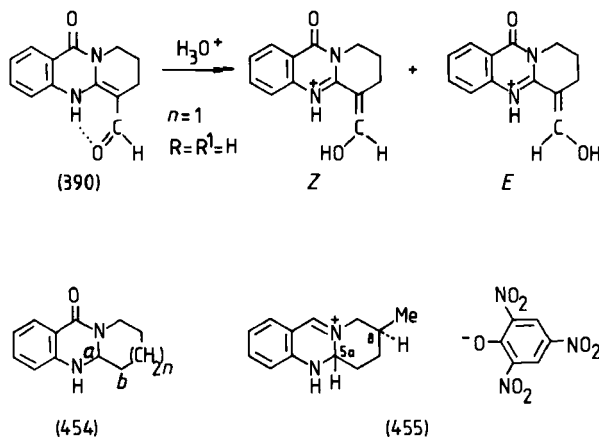


Horváth *et al.*³⁸³ reported that the tricyclic formyl derivatives **390** ($n = 0-2$) exhibit triple tautomerism between forms **451** and **453**. The imine-enamine-enol tautomerism depends greatly on the ring size (n). A significant solvent dependence was observed only for the pyrrolo[2,1-*b*]-quinazolinones **390** ($n = 0$), which in ethanolic solution exist predominantly in the imino form (**451**), and in chloroform in the enol form (**453**). ¹H-NMR spectroscopy showed that in chloroform the proportion of the imine tautomer **451** was about 5%. The fast equilibrium between the enamine and enol forms **452** and **453** was shifted considerably toward the enamine tautomer **452** in the case of the pyrido[2,1-*b*]quinazolinones **390** ($n = 1$). The azepino[2,1-*b*]quinazoline ($n = 2$, R = 2-NO₂) is a 2 : 3 mixture of the imine and the enamine tautomers **451** and **452**.



On protonation at the formyl oxygen atom, the 6-formyltetrahydropyrrodo[2,1-*b*]quinazolinone **390** ($n = 1$, R = R¹ = H) gave a 3 : 1 mixture of the *Z* and *E* geometric isomers of the enol form.³⁸³

The principal mass spectral fragmentation path for the homologous tricyclic derivatives **454** ($n = 0-2$) involves cleavage of the C—C bond between positions a and b (see structure), with subsequent loss of the methylene groups that formed the original cycloalkane ring.⁴⁰¹



The structures of octahydropyrido[2,1-*b*]quinazolinone hydrobromide (**283** · HBr)²⁷⁵ and the pyrido[2,1-*b*]quinazolinium picrate **455**⁴¹³ were determined by means of X-ray crystallography. The configuration of the latter was 5*aR*,8*S*, and two conformers were found in the crystal lattice.

Reports have been published on tricyclic derivatives of types **99**, **244**, and **333**, including their chromatographic (GC⁴¹⁴ and HPLC⁴¹⁵⁻⁴¹⁷) and polarographic behavior,⁴¹⁸ partition coefficients,⁴¹⁹⁻⁴²¹ and solubilities⁴²² in water, ethanol, and octanol, and also determination of their protonation constants.⁴²³

⁴¹³ G. Reck, E. Höhne, and G. Adam, *J. Prakt. Chem.* **316**, 496 (1974).

⁴¹⁴ Gy. Szász, O. Papp, J. Vámos, K. Hankó-Novák, and L. B. Kier, *J. Chromatogr.* **269**, 91 (1983).

⁴¹⁵ A. Shalaby, Zs. Budvári-Bárány, K. Hankó-Novák, Gy. Szász, and I. Hermecz, *Anal. Chem. Symp. Ser.* **16**, 165 (1984).

⁴¹⁶ A. Shalaby, Zs. Budvári-Bárány, and Gy. Szász, *J. Liq. Chromatogr.* **7**, 1133 (1984).

⁴¹⁷ A. Shalaby, Zs. Budvári-Bárány, Gy. Szász, and H. Bauer, *J. Liq. Chromatogr.* **7**, 1151 (1984).

⁴¹⁸ P. Pfeffel, C. Kühmstedt, F. Fülöp, and G. Bernáth, *Pharmazie* **39**, 106 (1984).

⁴¹⁹ Gy. Szász, K. Hankó-Novák, L. B. Kier, I. Hermecz, and J. Kökösi, *Acta Pharm. Hung.* **53**, 195 (1983) [*CA* **100**, 51009 (1984)].

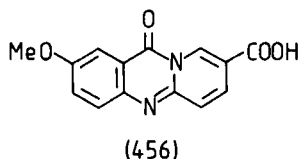
⁴²⁰ K. Hankó-Novák, Gy. Szász, O. Papp, J. Vámos, and I. Hermecz, *Acta Pharm. Hung.* **53**, 208 (1983) [*CA* **100**, 51010 (1984)].

⁴²¹ K. Hankó-Novák, Gy. Szász, M. Józán, Z. Mészáros, I. Hermecz, and L. B. Kier, *Intl. Symp. Med. Chem. Proc.*, 8th, 1984 **1**, 300 (1985).

⁴²² Zs. Halász-Ignáth, Gy. Szász, J. Kökösi, and I. Hermecz, *Acta Pharm. Hung.* **53**, 203 (1983) [*CA* **101**, 6515 (1984)].

⁴²³ K. Hankó-Novák, M. Józán, Gy. Szász, I. Hermecz, and J. Kökösi, *Acta Pharm. Hung.* **53**, 17 (1983) [*CA* **98**, 197500 (1983)].

An HPLC assay^{424,425} was developed for determination of the antiallergic 2-methoxy-11-oxo-pyrido[2,1-*b*]quinazoline-8-carboxylic acid (**456**).



E. APPLICATIONS

Pyrrolo[2,1-*b*]quinazolines have been patented as anticholinesterase,⁴²⁶ analgesic,^{255,358} antiallergic,^{255,355} antitussive,²⁵⁵ antipyretic,²⁵⁵ antiinflammatory,^{208,255,331} antiulcer,^{210,268} gastric secretion inhibitory,^{210,268} antithrombogenic,³³¹ blood platelet aggregation inhibitory,²⁷⁸ antidepressant,^{208,255} diuretic,^{255,331} hypotensive,^{208,278,358} and plant-growth inhibitory¹⁸⁴ agents.

Cyclopenta[*d*]pyrido[1,2-*a*]pyrimidines have been patented as tranquilizing,²⁶¹ antiallergic,²⁶⁸ and analgesic²⁴⁶ agents.

For pyrido[2,1-*b*]quinazolines the following biological effects are mentioned in patents: antiallergic,^{179,217,219,221,225,226,230,231,233-238,268,355} antiulcer,^{210,268} gastric secretion inhibitory,^{210,268} analgesic,^{230,231,246} antipyretic,^{230,231} antiinflammatory,^{208,230,231} hypotensive,^{208,278,370} blood platelet aggregation inhibitory,²⁷⁸ antidepressant,²⁰⁸ and nervous system depressive³⁷⁰ activities. Certain pyrido[2,1-*b*]quinazolines have been patented as intermediates for diuretic agents^{331,384} and red dyes,^{264,272} as sensitizers for azide photographic plates,⁴²⁷ an electron-acceptor sensitizers for poly(vinylcarbazole) or poly(vinylpyrine) photoconductors,^{263,428} and as fiber-reactive red dyes.³⁶⁷

Azepino[2,1-*b*]quinazolines have been patented as antidepressant,²⁰⁸ hypotensive,^{208,268} antiinflammatory,²⁰⁸ and blood platelet aggregation inhibitory²⁶⁸ agents.

Tricyclic derivatives of type **99** have been patented as intermediates for pharmaceuticals, pesticides, and dyes.¹⁸⁰

⁴²⁴ N. Strojny and J. A. De Silva, *J. Chromatogr.* **179**, 311 (1979).

⁴²⁵ N. Strojny and J. A. De Silva, *Anal. Chem.* **52**, 1554 (1980).

⁴²⁶ S. Yu. Yunusov, N. Tulyaganov, M. V. Telezhenetskaya, F. Sadritdinov, and Kh. Khashimov, U.S.S.R. Patent 605,614 [*CA* **89**, 100346 (1978)].

⁴²⁷ G. A. Reynolds, E. M. Robertson, and J. A. Van Allan, U.S. Patent 3,072,485 [*CA* **58**, 10903b (1963)].

⁴²⁸ J. Hagendorn and H. Knibbe, German Patent 2,525,381 [*CA* **84**, 172154 (1976)].

The biological properties of vasicine (184) and vasicinone (185) have been studied in some detail. Vasicine (184) was investigated for antispasmodic,⁸⁹ cholegogic,⁴²⁹ antimicrobial,⁴³⁰ and anthelmintic⁹⁶ activities. Its effects on the circulation¹⁰³ and on the peristaltic and secretory functions of the gastrointestinal tract⁴³¹ have also been studied, as has the anthelmintic effect of vasicinone (185).⁹⁶

Vasicinone (185) exhibited bronchodilator,^{91,107,365,432-436} weak cardiac stimulant,⁴³⁵ and potent antianaphylactic⁴³⁵ activities, whereas vasicine (184) displayed bronchoconstrictor^{91,319,432} and cardiac depressant activities.⁴³⁵ The structure-bronchodilator activity relationship was discussed.⁴³² Vasicine (184) also had marked respiratory and uterine stimulant activities and a moderate hypotensive activity.^{159,437} Vasicinone (185) was devoid of these activities.⁴³⁷

The uterotonic activity of vasicine (184) was investigated in detail on the uteri of different animal⁴³⁸ species and on human myometrium.⁴³⁹ The uterotonic effect of vasicine (184) was similar to those of oxytocin and methyletergometrine.⁴³⁸ Vasicine hydrochloride (184 · HCl) potentiated the oxytocin-induced contraction of isolated rat and rabbit uterus⁴⁴⁰ and rat mammary gland strips.^{440,441} The thrombocytopoietic activity⁴⁴² of vasicine hydrochloride (184 · HCl), its absorption and distribution in mice,⁴⁴³ its

⁴²⁹ M. I. Rabinovich, A. I. Leskov, and A. S. Gladkikh, *Mater. Konf. Fiziol., Biokhim. Farmakol. Vchastiem Prakt. Vrach., Ufa*, 181 (1966) [CA 67, 10191 (1967)].

⁴³⁰ I. Isamukhamedov, *Farmakol. Alkaloidov Ikh Proizvodnykh.*, 185 (1972) [CA 80, 116598 (1974)].

⁴³¹ M. I. Rabinovich and L. G. Pavlik, *Tr. Troitsk. Vet. Inst.* 9, 79 (1965) [CA 66, 54165 (1967)].

⁴³² A. H. Amin, D. R. Mehta, and S. S. Samarth, *Proc. Int. Pharmacol. Meet. 1st, 1961*, Vol. 7, p. 377 (1962) [CA 61, 7537c (1964)].

⁴³³ M. B. Bhide, P. Y. Naik, S. S. Mahajani, R. B. Ghooi, and R. S. Joshi *Bull. Haffkine Inst.* 2, 6 (1974) [CA 82, 38618 (1975)].

⁴³⁴ M. B. Bhide and S. S. Mahajani, *Bull. Haffkine Inst.* 3, 128 (1975) [CA 85, 375 (1976)].

⁴³⁵ M. B. Bhide, P. Y. Naik, and R. B. Ghooi, *Bull. Haffkine Inst.* 4, 43 (1976) [CA 85, 153929 (1976)].

⁴³⁶ H. L. Bhalla and A. Y. Nimbkar, *Drug Dev. Ind. Pharm.* 8, 833 (1982).

⁴³⁷ O. P. Gupta, M. L. Sharma, B. J. R. Ghatak, and C. K. Atal, *Indian J. Med. Res.* 66, 680 (1977).

⁴³⁸ O. P. Gupta, M. L. Sharma, B. J. R. Ghatak, and C. K. Atal, *Indian J. Med. Res.* 66, 865 (1977).

⁴³⁹ O. P. Gupta, R. L. Wakhlov, M. L. Sharma, and C. K. Atal, *J. Obstet. Gynaecol. India* 29, 935 (1979).

⁴⁴⁰ C. S. Gantam and P. L. Sharma, *Indian J. Med. Res.* 76, Suppl., 107 (1982).

⁴⁴¹ C. S. Gautam and P. L. Sharma, *Bull. Postgrad. Inst. Med. Educ. Res., Chandigarh* 16, 122 (1982) [CA 99, 419 (1983)].

⁴⁴² C. K. Atal, M. L. Sharma, A. Khajuria, and A. Kaul, *Indian J. Exp. Biol.* 20, 704 (1982).

⁴⁴³ V. Zutshi, P. G. Rao, A. Soni, O. P. Gupta, and C. K. Atal, *Planta Med.* 40, 373 (1980).

compatibility, stability,⁴⁴⁴ and metabolism in rats,⁴⁴⁵ and its cumulative properties⁴⁴⁶ have also been investigated. *Piper longum* (long pepper) increased the blood levels of vasicine (184).⁴⁴⁷

Vasicine hydrochloride (184 · HCl) given to pregnant volunteers was well tolerated.⁴⁴⁸ Its intraamniotic injection was effective in inducing mid-trimester abortions.⁴⁴⁹

The stability,^{449,450} compatibility,^{444,451} and toxicity in mice,⁴⁵² the absorption in dogs,^{436,452} and the effect of antacids on the availability⁴⁵³ of vasicinone (185) have likewise been studied. Its solubility, intrinsic dissolution rate, dissociation constant, and partition coefficient have been determined.⁴⁵⁴

Peganol (186) displayed anticholinesterase activity⁴⁵⁵ and inhibited aurogenic reactions in rats.⁴⁵⁶

Deoxyvasicine (124) showed antihypertensive activity in neurogenic hypertensive dogs.⁵⁷ Deoxyvasicine hydrochloride was tested for toxicity.⁴⁵⁷ Deoxyvasicinone (95) exhibited antiinflammatory properties.⁴⁵⁸ The metabolisms of these two compounds were studied in rats.^{398,459} The biotransformation of deoxyvasicine (124) goes through deoxyvasicinone (95). Identified metabolites include: 1- and 3-hydroxytetrahydropyrrolo[2,1-*b*]quinazolinones (457 and 185), 7-methoxydihydropyrrolo[2,1-*b*]quinazolinone (458) (the position of the double bond in the pyrrole ring was not definitely determined, and a quinazoline derivative (459).

⁴⁴⁴ H. L. Bhalla, *Indian J. Hosp. Pharm.* **19**, 24 (1982).

⁴⁴⁵ S. C. Sharma, M. A. Siddigi, U. Zutshi, and C. K. Atal, *Indian Drugs* **20**, 431 (1983).

⁴⁴⁶ A. D. Puzii and G. A. Tsyganova, *Mery Profil. Ter. Zabol. S.-kh. Zhivotn. Frunze*, 98 (1979) [CA **94**, 25048 (1981)].

⁴⁴⁷ C. K. Atal, U. Zutshi, and P. G. Rao, *J. Ethnopharmacol.* **4**, 229 (1981).

⁴⁴⁸ R. L. Wakhlov, G. Kaul, O. P. Gupta, and C. K. Atal, *Indian J. Pharmacol.* **12**, 129 (1980).

⁴⁴⁹ R. L. Wakhlov, D. Wakhlov, O. P. Gupta, and C. K. Atal, *J. Obstet. Gynaecol. India* **29**, 939 (1979).

⁴⁵⁰ H. L. Bhalla, *Indian Drugs* **19**, 143 (1982).

⁴⁵¹ H. L. Bhalla, *Indian Drugs* **18**, 327 (1981).

⁴⁵² H. L. Bhalla, *Indian J. Pharm. Sci.* **43**, 221 (1981).

⁴⁵³ H. L. Bhalla, *Indian Drugs* **19**, 1 (1982).

⁴⁵⁴ H. L. Bhalla, *Drug Dev. Ind. Pharm.* **7**, 75 (1981).

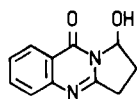
⁴⁵⁵ B. Rustamov, N. Tulyaganov, and F. Sadritdinov, *Med. Zh. Uzb.*, 22 (1974) [CA **83**, 90803 (1975)].

⁴⁵⁶ G. V. Arkhipova, E. B. Burlakova, A. F. Semiokhin, I. B. Fedotova, and L. V. Krushinskii, *Dokl. Akad. Nauk SSSR* **267**, 469 (1982) [CA **98**, 101167 (1983)].

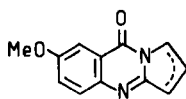
⁴⁵⁷ V. V. Muratova, R. A. Ashrafova, and F. S. Sadritdinov, *Med. Zh. Uzb.*, 53 (1984) [CA **100**, 132532 (1984)].

⁴⁵⁸ D. B. Reisner, B. J. Ludwig, E. Simon, T. Dejneka, and R. D. Sofia, *Arzneim.-Forsch.* **27**, 766 (1977).

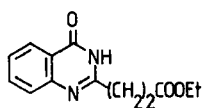
⁴⁵⁹ V. N. Plugar, Ya. V. Rashkes, and N. Tulyaganov, *Khim. Prir. Soedin.*, 201 (1981) [CA **95**, 163177 (1981)].



(457)



(458)

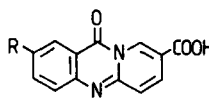


(459)

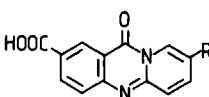
The pharmacological actions of peganidine (**189**) and deoxypeganidine (**190**) were investigated.⁴⁶⁰ Both compounds potentiated the physiological effects of acetylcholine and nicotine and inhibited cholinesterase *in vitro*.

The tetrahydropyrido[2,1-*b*]quinazolinone **203** exhibited antiinflammatory properties.⁴⁶¹

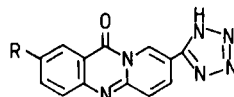
Among the pyrido[2,1-*b*]quinazolinecarboxylic acids, the 2- and 8-carboxylic acids had significant antiallergic activities.^{220,223,227,239} The 2-substituted pyridoquinazoline-8-carboxylic acids **460**^{220,223,227} and 8-substituted pyridoquinazoline-2-carboxylic acids **461**²²⁰ were found to be orally active in rat passive cutaneous anaphylaxis and rat allergic bronchospasm models.



(460)



(461)



(462)

The mediator release inhibitors **460** and **461** were shown to inhibit human leucocyte alkaline phosphatase noncompetitively.^{227,462} As substituents, methyl, isopropyl, and methoxy were found optimal for **460**, and methyl and isopropyl for **461**.

The 8-(5-tetrazolyl)pyrido[2,1-*b*]quinazolinones (**462**) also had antiallergic activities when administered intravenously in mice.²²⁷

The inhibitory activities of 11-oxopyrido[2,1-*b*]quinazolinecarboxylic acids on rat lens and human placental aldose reductase were studied.⁴⁶³ From the specific structural and electronic similarities of diverse aldose reductate inhibitors the pharmacophore requirements for an inhibitor were postulated.⁴⁶⁴

The antiallergic 2-methoxy-11-oxopyrido[2,1-*b*]quinazoline-8-carboxy-

⁴⁶⁰ N. Tulyaganov, *Farmakol. Priir. Veshchestv.*, 56 (1978) [CA **91**, 234 (1979)].

⁴⁶¹ J. Maillard, M. Benard, M. Vincent, Vo Van Tri, R. Jolly, R. Morin, C. Menillet, and M. Benharkate, *Chim. Ther.* **2**, 202 (1967).

⁴⁶² Ch. F. Schwender, *Biochem. Pharmacol.* **30**, 217 (1981).

⁴⁶³ P. F. Kador, N. E. Sharpless, and J. D. Goosey, *Prog. Clin. Biol. Res.* **114**, 273 (1982).

⁴⁶⁴ P. F. Kador and N. E. Sharpless, *Mol. Pharmacol.* **24**, 521 (1983).

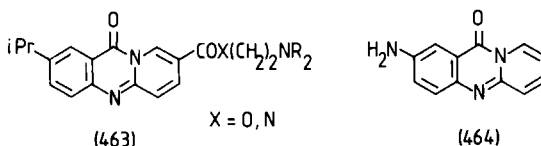
lic acid **456** was selected for further pharmacological and clinical examination.⁴⁶⁵⁻⁴⁶⁹

2-Methoxyprido[2,1-*b*]quinazoline-8-carboxylic acid (**456**) was a potent inhibitor of antigen-induced, compound 48/80-induced, and concavalin A-induced histamine release from rat peritoneal cells.^{466,467} It also inhibited antigen-induced release of histamine and slow-reacting substances of anaphylaxis from actively sensitized guinea pig lung fragments.⁴⁶⁶ The effect of **456** on the phosphorylation of a single mast cell protein was examined.⁴⁶⁹ A specific radioimmunoassay was developed to determine the plasma concentrations of **456** in man following oral administration.⁴⁶⁵

The pharmacokinetic profile of compound **456** in man following oral doses was investigated.⁴⁶⁸

2-Methoxypridoquinazoline-8-carboxylic acid (**456**) inhibited thromboxane A₂ production by preventing the release of histamine and the synthesis of SRS-A in the perfused lung system.⁴⁷⁰

Basic esters and amides of 2-isopropylprido[2,1-*b*]quinazoline-8-carboxylic acid (**463**) were evaluated for their ability to prevent SRS-A-induced contractions of guinea pig ileum.²²⁴



In a study of the mutagenicity of the antiasthmatic pyrido[2,1-*b*]quinazolinones **286** and **464**, the amino derivative **464** proved to be a strong mutagen.⁴⁷¹

The hexahydroazepino[2,1-*b*]quinazolinone **306** showed the maximum bronchodilatory activity from among the homologous tricyclic derivatives **99** ($n = 0-2$).¹⁵⁹

Among the tricyclic derivatives of types **99**, **244** ($R = H$; $R^1 = H, Me$), **248**, and **333** ($R = H$; $R^1 = H, Me$), the azepino derivatives **465** and **466** had

⁴⁶⁵ R. Dixon, R. Lucek, Y.-Y. Lin, W. Colburn, and M. Parsonnet, *Res. Commun. Chem. Pathol. Pharmacol.* **30**, 163 (1980).

⁴⁶⁶ A. F. Welton, W. C. Hope, H. J. Crowley, and R. A. Salvador, *Agents Actions* **11**, 345 (1981).

⁴⁶⁷ R. A. Salvador, L. B. Czyzewski, H. Baruth, A. Hooper, A. Medford, D. Miller, T. Van Trabert, B. Yaremko, and A. F. Welton, *Agents Actions* **11**, 339 (1981).

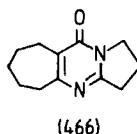
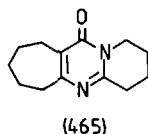
⁴⁶⁸ W. A. Colburn, R. Lucek, R. Dixon, and M. Parsonnet, *Drugs Exp. Clin. Res.* **7**, 609 (1981).

⁴⁶⁹ W. Sieghart, T. C. Theoharides, W. W. Douglas, and P. Greengard, *Biochem. Pharmacol.* **30**, 2737 (1981).

⁴⁷⁰ A. F. Welton, H. J. Crowley, G. Folco, and T. Vigano, *Agents Actions* **12**, 438 (1982).

⁴⁷¹ M. A. Jimenez, M. Torroella, S. I. Fernandez, and R. Pellon, *Mutat. Res.* **117**, 225 (1983).

the maximum bronchodilatory activity.^{472,473} These compounds displayed their effects in part as phosphodiesterase inhibitors.⁴⁷⁴

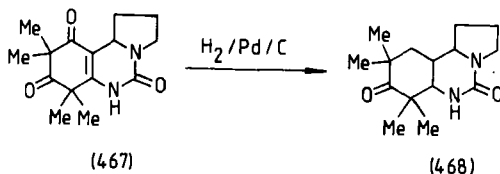


The formation of compounds of type **257** was utilized for the identification and determination of Δ^1 -pyrroline and its homologs and open-chain analogs.^{283,285-296, 298,303,304,362,475,476}

VI. Appendix

A. ANGULAR ANNELATED RING SYSTEMS WITH NITROGEN AWAY FROM THE RING ANGLE (TYPE I)

Hufford *et al.*⁴⁷⁷ isolated syncarpurea (**467**) from *Uvaria afzelii* and determined its structure by X-ray diffraction. Syncarpurea (**467**) was hydrogenated to pyrrolo[1,2-*c*]quinazolinone (**468**) over palladium on carbon in ethanol under a pressure of 30 psi; the product was then N-acylated with acetic anhydride. Structures were characterized by UV, IR, ¹H- and ¹³C-NMR spectroscopy.



Potts *et al.*⁴⁷⁸ reported that the mesoinoic thiazo[3,2-*c*]quinazoline **469** underwent cycloaddition with dimethyl fumarate and ethyl acrylate in refluxing xylene to give the dihydropyrrolo[1,2-*a*]quinazolines **470** and **473**.

⁴⁷² I. Hermecz, L. Vasvári-Debreczy, Á. Horváth, T. Breining, C. DeVos, and L. Rodriguez, *Intl. Symp. Med. Chem. Proc.*, 8th, 1984 **2**, 148 (1985).

⁴⁷³ I. Hermecz, L. Vasvári-Debreczy, Á. Horváth, S. Virág, T. Breining, and J. Kökösi, German Patent 3,339,635 [CA **101**, 130705 (1984)].

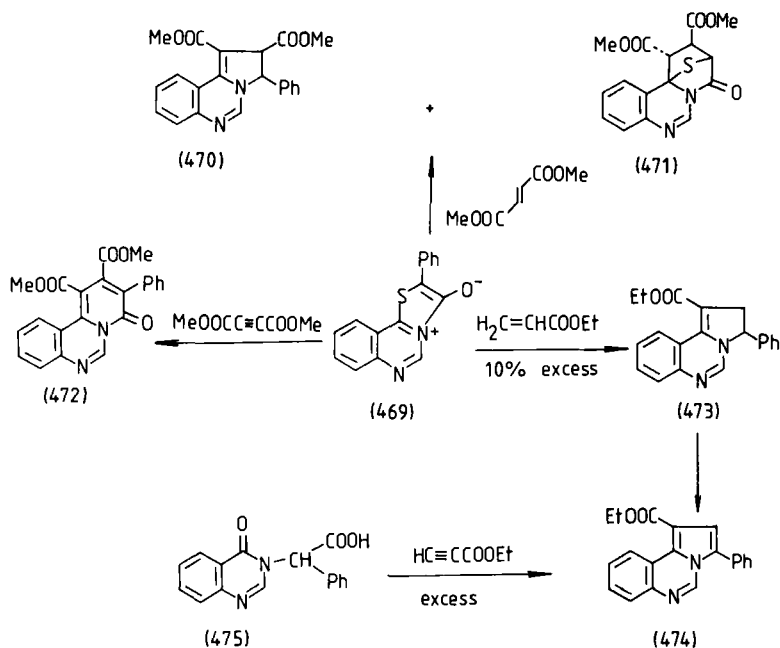
⁴⁷⁴ K. Ajtai, G. Hegyi, K. Tuka, I. Stadler, I. Hermecz, and K. Takács, *Drugs, Biochem. Metab., Sci. Mater. Pap. Collog.*, 1981, 73 (1981) [CA **96**, 115748 (1982)].

⁴⁷⁵ S. Sakamoto, N. Shibahara, and K. Samejime, *Bunseki Kagaku* **32**, 669 (1983) [CA **98**, 194340 (1983)].

⁴⁷⁶ R. L. Larson, W. D. Sandine, and H. P. Broquist, *J. Biol. Chem.* **238**, 275 (1963).

⁴⁷⁷ C. D. Hufford, B. Oguntimein, M. Martin, and J. Clardy, *Tetrahedron Lett.* **25**, 371 (1984).

⁴⁷⁸ K. T. Potts, K. Bordeaux, W. Kuehnling, and R. Salsbury, *Chem. Commun.*, 213 (1984).



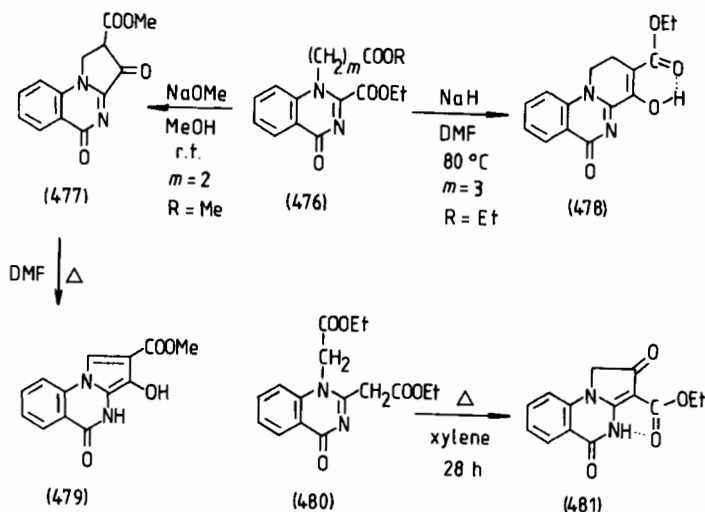
From the reaction with dimethyl fumarate, the 1 : 1 cycloadduct **471** was also isolated. On oxidation with 2,3,5,6-dichlorodicyanobenzoquinone in boiling dioxane, dihydropyrrolo[1,2-*a*]quinazoline-1-carboxylate (**473**) afforded the pyrrolo[1,2-*a*]quinazoline-1-carboxylate **474**. The latter product also resulted when the acid **475** was treated with an excess of ethyl propiolate and acetic anhydride in boiling xylene. The reaction of the thiazo[3,2-*c*]quinazoline **469** with dimethyl acetylenedicarboxylate in boiling toluene led to the pyrimido[1,2-*a*]quinazolinone **472**.

B. ANGULAR ANNELETED RING SYSTEMS WITH NITROGEN IN THE RING ANGLE (TYPE II)

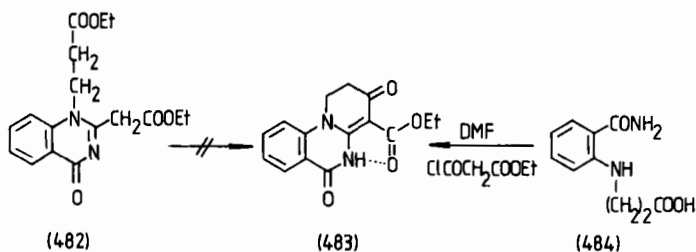
Yamada and co-workers⁴⁷⁹ prepared the pyrrolo- and pyrido[1,2-*a*]quinazolinones **477**, **478**, and **481** from the diesters **476** and **480** by Dieckmann condensation.

When heated in dimethylformamide, the tetrahydropyrrolo[1,2-*a*]quinazolin-3-one **477** isomerized to the dihydropyrrolo[1,2-*a*]quinazolin-3-ol **479**. The pyrimido[1,2-*a*]quinazolinone **483** resulted from the reaction of 3-[(O-carbamoylphenyl)amino]propionic acid (**484**) with ethyl chloro-

⁴⁷⁹ K. Ozaki, Y. Yamada, and T. Oine, *Chem. Pharm. Bull.* **31**, 2234 (1983).



formylacetate in dimethylformamide at 50°C. Cyclization of the diester **482** to **483** was unsuccessful.



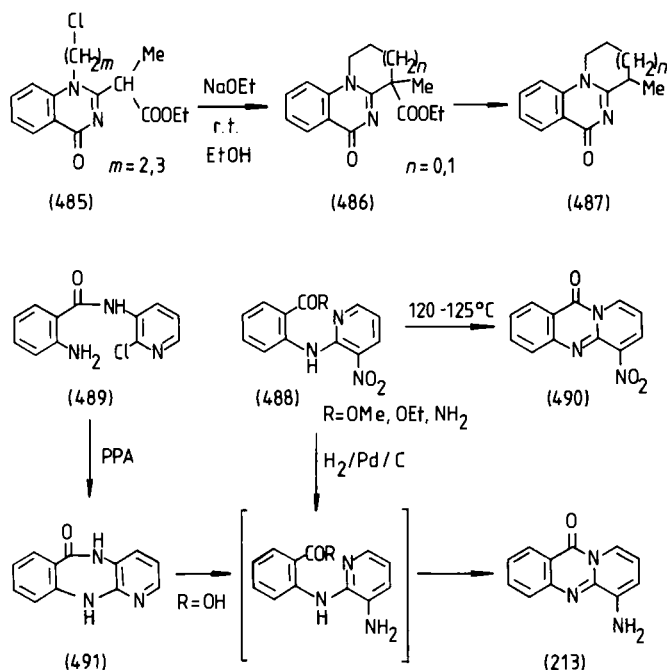
The quinazolinones **485** were cyclized to the tricyclic esters **486** by reaction with sodium ethoxide in ethanol at ambient temperature. When the tricyclic esters **486** were hydrolyzed with potassium hydroxide and subsequently acidified, decarboxylation took place spontaneously to give **487**.

C. LINEARLY ANNELATED RING SYSTEMS (TYPE III)

From the reaction of 2-chlorobenzoic acid and 2-amino-5-nitropyridine in the presence of potassium carbonate and copper powder or copper(II) oxide, Carboni and Pardi⁴⁰³ isolated the condensation product **210** ($R = H$, $R^1 = 5\text{-NO}_2$), which was then cyclized with a strong concentrated acid to the pyrido[2,1-*b*]quinazoline **211** ($R = H$, $R^1 = 8\text{-NO}_2$).

In the reaction of 2-chloro-3-nitropyridine and alkyl anthranilate or

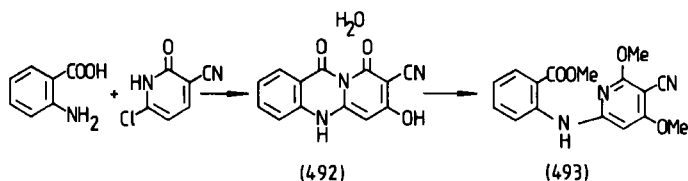
anthranilamide in the presence of potassium fluoride at 170°C, Kovač *et al.*⁴⁸⁰ prepared the condensation product **488**, which was cyclized to 6-nitropyrido[2,1-*b*]quinazolinone (**490**) in a 1 : 1 mixture of dioxane and acetic acid at 120–125°C, and to 6-aminopyrido[2,1-*b*]quinazolinone (**213**) during hydrogenation over palladium on carbon in dioxane. Besides pyrido[2,3-*b*][1,4]benzodiazepine (**491**), the amino derivative (**213**) was obtained when 3-(*o*-aminobenzoylamido)-2-chloropyridine (**489**) was heated in polyphosphoric acid at 160°C in the presence of ammonium chloride.



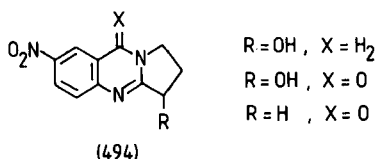
Reisch *et al.*⁴⁸¹ stated that 6-chloro-3-cyanopyridin-2(1*H*)-one and anthranilic acid in acetic acid or in dimethylformamide in the presence of potassium carbonate and copper powder gave the hydrate of pyrido[2,1-*b*]quinazolinone (**492**). When compound **492** was treated with diazomethane, a ring-opened product (**493**) was obtained.

⁴⁸⁰ T. Kovač, M. Oklobdžija, G. Comisso, E. Decorte, T. Fajdiga, F. Moimas, C. Angeli, F. Zonno, R. Toso, and V. Šunjić, *J. Heterocycl. Chem.* **20**, 1339 (1983).

⁴⁸¹ J. Reisch, S. M. El-Moghazy Aly, and I. Mester, *Arch. Pharm. (Weinheim, Ger.)* **317**, 824 (1984).



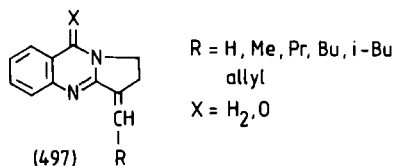
Nitration of vasicine (**184**), vasicinone (**185**), and deoxyvasicinone (**95**) gave the corresponding 7-nitro derivatives (**494**).⁴⁸²



The diamines **495** gave the antiallergic pyrido[2,1-*b*]-1*H*-triazolo-[4,5-*g*]quinazolinones **496** by reaction with diphenylnitrosamine at 75–85°C in the presence of sodium acetate in acetic acid or with sodium nitrite at 40°C in aqueous acetic acid.⁴⁸³



Rao *et al.*⁴⁸⁴ obtained the condensation products **497** with aliphatic aldehydes from vasicine (**184**) and vasicinone (**185**) if the reactions were carried out under pressure in xylene at 140°C.



⁴⁸² M. P. Join, C. K. Atal, R. Bandhyopadhyay, and B. G. Nagari, *Indian J. Pharm. Sci.* **45**, 178 (1983).

⁴⁸³ K. Schromm, A. Mentrup, E. O. Renth, and A. Fügner, German Patent 3,300,477 [CA **101**, 191963 (1984)].

⁴⁸⁴ M. N. A. Rao, S. Krishnan, M. P. Jain, and K. K. Anand, *Indian J. Pharm. Sci.* **44**, 151 (1982).

Note Added in Proof

Much recent work on tricyclic compounds with a central pyrimidine ring and one bridgehead nitrogen has come to the attention of the authors since this chapter was submitted for publication. The work cannot be discussed in detail, but it was felt that references should be provided.⁴⁸⁵⁻⁵⁰⁴

ACKNOWLEDGMENTS

We would like to thank Dr. D. Durham for linguistic improvements, and Dr. M. Balogh and Mrs. G. Mile-Gazdag for technical assistance.

- ⁴⁸⁵ K. T. Okamoto and J. Clardy, *Tetrahedron Lett.* **25**, 2937 (1984).
⁴⁸⁶ K. Hankó-Novák, M. Józán, Gy. Szász, J. Kökösi, and I. Hermecz, *Acta Pharm. Hung.* **54**, 280 (1984) [*CA* **102**, 184458 (1985)].
⁴⁸⁷ A. D. Dunn and K. I. Kinnear, *J. Heterocycl. Chem.* **22**, 311 (1985).
⁴⁸⁸ C. Kaneko, T. Chiba, K. Kasai, and C. Miwa, *Heterocycles* **23**, 1385 (1985).
⁴⁸⁹ A. Shalaby, Zs. Budvári-Bárány, Gy. Szász, K. Hankó-Novák, and I. Hermecz, *J. Liq. Chromatogr.* **8**, 381 (1985).
⁴⁹⁰ A. Shalaby, Zs. Budvári-Bárány, and Gy. Szász, *J. Liq. Chromatogr.* **8**, 1071 (1985).
⁴⁹¹ A. Shalaby, Zs. Budvári-Bárány, and Gy. Szász, *J. Liq. Chromatogr.* **8**, 1093 (1985).
⁴⁹² K. Hankó-Novák, Gy. Szász, and M. Józán, *Magy. Kém. Foly.* **90**, 563 (1984) [*CA* **102**, 148621 (1985)].
⁴⁹³ I. Hermecz, J. Kökösi, L. Vasvári-Debreczy, Á. Horváth, B. Podányi, Gy. Szász, and Z. Mészáros, *Intl. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. [Proc.]*, 3rd, 1985, **5**, 332 (1985).
⁴⁹⁴ K. T. Potts, K. G. Bordeaux, W. R. Kuehnling, and R. L. Salisbury, *J. Org. Chem.* **50**, 1666 (1985).
⁴⁹⁵ T. Higashino, H. Kobuko, and E. Hayashi, *Chem. Pharm. Bull.* **33**, 950 (1985).
⁴⁹⁶ V. N. Gupta, V. K. Gupta, C. K. Atal, H. Shah, and B. G. Nagari, *Indian J. Pharm. Sci.* **46**, 89 (1984).
⁴⁹⁷ G. Doria, C. Passarotti, R. Magrini, R. Sala, P. Sberze, M. Tibolla, G. Arcari, R. Ceserani, and R. Castello, *Farmaco, Ed. Sci.* **39**, 968 (1984).
⁴⁹⁸ E. Santaniello, A. Manzocchi, P. A. Biondi, C. Secchi, and T. Simonic, *Chem. Commun.*, 803 (1984).
⁴⁹⁹ W. Verboom, M. R. J. Hamzink, D. N. Reinhoudt, and R. Visser, *Tetrahedron Lett.* **25**, 4309 (1984).
⁵⁰⁰ N. Strojny, C. V. Puglisi, and J. A. De Silva, *J. Chromatogr.* **336**, 301 (1984).
⁵⁰¹ S. Khakimdzhanov, A. L. Kats, Kh. S. Umarov, and S. S. Kasymova, *Dokl. Akad. Nauk. Uzb. SSR*, 37 (1984) [*CA* **102**, 105092 (1985)].
⁵⁰² J. C. Barnes, J. N. Low, J. D. Paton, A. D. Dunn, and K. J. Kinnear, *Acta Crystallogr. Sect. C, Cryst. Struct. Commun.* **C41**, 282 (1985).
⁵⁰³ R. R. V. Krishna, T. Satyanarayana, and R. B. V. Kameswara, *Fitoterapia* **55**, 249 (1984).
⁵⁰⁴ A. Kh. Sattarova, E. K. Dobronravova, and T. T. Shakirov, *Khim. Prir. Soedin.*, 84 (1985) [*CA* **102**, 191228n (1985)].

This Page Intentionally Left Blank

Cumulative Index of Titles

A

Acetylenecarboxylic acids and esters, reactions with *N*-heterocyclic compounds, **1**, 125
 Acetylenecarboxylic esters, reactions with nitrogen-containing heterocycles, **23**, 263
 Acetylenic esters, synthesis of heterocycles through nucleophilic additions to, **19**, 297
 Acid-catalyzed polymerization of pyrroles and indoles, **2**, 287
t-Amino effect, **14**, 211
 Aminochromes, **5**, 205
 Anils, olefin synthesis with, **23**, 171
 Annelation of a pyrimidine ring to an existing ring, **32**, 1
 Annulenes, N-bridged, cyclazines and, **22**, 321
 Anthracen-1,4-imines, **16**, 87
 Anthranils, **8**, 277; **29**, 1
 Applications of NMR spectroscopy to indole and its derivatives, **15**, 277
 Applications of the Hammett equation to heterocyclic compounds, **3**, 209; **20**, 1
 Arene oxides, chemistry of, **37**, 67
 Aromatic azapentalenes, **22**, 183
 Aromatic quinolizines, **5**, 291; **31**, 1
 Aromaticity of heterocycles, **17**, 255
 Aza analogs of pyrimidine and purine bases, **1**, 189
 7-Azabicyclo[2.2.1]hepta-2,5-dienes, **16**, 87
 1-Azabicyclo[3.1.0]hexanes and analogs with further heteroatom substitution, **27**, 1
 Azapentalenes, aromatic, chemistry of, **22**, 183
 8-Azapurines, chemistry of, **39**, 117
 Azines, reactivity with nucleophiles, **4**, 145

Azines, theoretical studies of, physicochemical properties of reactivity of, **5**, 69
 Azinoazines, reactivity with nucleophiles, **4**, 145
 Aziridines, application to synthesis of natural products, **39**, 181
 1-Azirines, synthesis and reactions of, **13**, 45
 Azodicarbonyl compounds in heterocyclic synthesis, **30**, 1

B

Barbituric acid, recent progress in chemistry of, **38**, 229
 Base-catalyzed hydrogen exchange, **16**, 1
 1-, 2-, and 3-Benzazepines, **17**, 45
 Benzisothiazoles, **14**, 43; **38**, 105
 Benzisoxazoles, **8**, 277
 Benzoazines, reactivity with nucleophiles, **4**, 145
 Benzo[*c*]cinnolines, **24**, 151
 1,5-Benzodiazepines, **17**, 27
 Benzo[*b*]furan and derivatives, recent advances in chemistry of, Part 1, occurrence and synthesis, **18**, 337
 Benzo[*c*]furans, **26**, 135
 Benzo[*f*]uroxans, **10**, 1; **29**, 251
 2*H*-Benzopyrans (chrom-3-enes), **18**, 159
 Benzothiazines
 1,2- and 2,1-benzothiazines and related compounds, **28**, 73
 1,4-benzothiazines and related compounds, **38**, 135
 Benzo[*b*]thiophene chemistry, recent advances in, **11**, 177; **29**, 171
 Benzo[*c*]thiophenes, **14**, 331
 1,2,3-(Benzo)triazines, **19**, 215

Benzyne, reactions with heterocyclic compounds, 28, 183
Biological pyrimidines, tautomerism and electronic structure of, 18, 199
Bipyridines, 35, 281
Bridgehead nitrogen, tricyclic compounds with a central pyrimidine ring and, 39, 281

C

9*H*-Carbazoles, recent advances in, 35, 83
Carbenes
 and nitrenes, intramolecular reactions, 28, 231
 reactions with heterocyclic compounds, 3, 57
Carbolines, 3, 79
Cationic polar cycloaddition, 16, 289 (19, xi)
Chemistry
 of arene oxides, 37, 67
 of aromatic azapentalenes, 22, 183
 of barbituric acid, recent progress in, 38, 229
 of benzo[*b*]furan, Part I, occurrence and synthesis, 18, 337
 of benzo[*b*]thiophenes, 11, 177; 29, 171
 of chrom-3-enes, 18, 159
 of diazepines, 8, 21
 of dibenzothiophenes, 16, 181
 of dihydroazines, 38, 1
 of 1,2-dioxetanes, 21, 437
 of furans, 7, 377
 of hydantoins, 38, 177
 of isatin, 18, 1
 of isoxazolidines, 21, 207
 of lactim ethers, 12, 185
 of mononuclear isothiazoles, 14, 1
 of 4-oxy- and 4-keto-1,2,3,4-tetrahydro-isoquinolines, 15, 99
 of phenanthridines, 13, 315
 of phenothiazines, 9, 321
 of polycyclic isothiazoles, 38, 1
 of 1-pyridines, 15, 197
 of pyrrolizines, 37, 1
 of tetrazoles, 21, 323
 of 1,3,4-thiadiazoles, 9, 165
 of thienothiophenes, 19, 123
 of thiophenes, 1, 1

Chrom-3-ene chemistry, advances in, 18, 159
Claisen rearrangements, in nitrogen heterocyclic systems, 8, 143
Complex metal hydrides, reduction of nitrogen heterocycles with, 6, 45; 39, 2
Covalent hydration
 in heteroaromatic compounds, 4, 1, 43
 in nitrogen heterocycles, 20, 117
Current views on some physicochemical aspects of purines, 24, 215
Cyclazines, and related N-bridged annulenes, 22, 321
Cyclic enamines and imines, 6, 147
Cyclic hydroxaminic acids, 10, 199
Cyclic peroxides, 8, 165
Cyclizations under Vilsmeier conditions, 31, 207
Cycloaddition, cationic polar, 16, 289, (19, xi)
(2 + 2)-Cycloaddition and (2 + 2)-cycloreversion reactions of heterocyclic compounds, 21, 253

D

Developments in the chemistry
 of furans (1952–1963), 7, 377
 of Reissert compounds (1968–1978), 24, 187
Dewar heterocycles and related compounds, 31, 169
2,4-Dialkoxypyrimidines, Hilbert–Johnson reaction of, 8, 115
Diazepines, chemistry of, 8, 21
1,4-Diazepines, 2,3-dihydro-, 17, 1
Diazirines, diaziridines, 2, 83; 24, 63
Diazo compounds, heterocyclic, 8, 1
Diazomethane, reactions with heterocyclic compounds, 2, 245
Dibenzothiophenes, chemistry of, 16, 181
Dihydroazines, recent advances in chemistry of, 38, 1
Dihydro-1,4-benzothiazines, and related compounds, 38, 135
2,3-Dihydro-1,4-diazepines, 17, 1
1,2-Dihydroisoquinolines, 14, 279
1,2-Dioxetanes, chemistry of, 21, 437
Diquinolylmethane and its analogs, 7, 153

gem-Dithienylalkanes and their derivatives,
32, 83
1,2- and 1,3-Dithiolium ions, 7, 39; 27, 151
1,3-Dithiol-3-thiones and 1,2-dithiol-3-ones,
31, 63

E

Electrochemical synthesis of pyridines, 37,
167
Electrolysis of *N*-heterocyclic compounds
part I, 12, 213
part II, 36, 235
Electronic aspects of purine tautomerism,
13, 77
Electronic structure of biological
pyrimidines, tautomerism and, 18, 199
Electronic structure of heterocyclic sulfur
compounds, 5, 1
Electrophilic substitutions of five-membered
rings, 13, 235
 β -Enamino esters, heterocyclic, as
heterocyclic synthons, 38, 299
 π -Excessive heteroannulenes, medium-large
and large, 23, 55

F

Ferrocenes, heterocyclic, 13, 1
Five-membered rings, electrophilic
substitutions of, 13, 235
Formation of anionic σ -adducts from
heteroaromatic compounds, 34, 305
Free radical substitutions of heteroaromatic
compounds, 2, 131
Furans
development of the chemistry of
(1952–1963), 7, 377
dibenzo-, 35, 1
recent advances in chemistry, Part I, 30,
167
Furoxans, 29, 251

G

Grignard reagents, indole, 10, 43

H

Halogenation of heterocyclic compounds, 7,
1
Hammett equation, applications to
heterocyclic compounds, 3, 209; 20, 1
Hetarynes, 4, 121
Heteroadamantane, 30, 79
Heteroannulenes, medium-large and large
 π -excessive, 23, 55
Heteroaromatic compounds
N-aminoazonium salts, 29, 71
free-radical substitutions of, 2, 131
homolytic substitution of, 16, 123
nitrogen, covalent hydration in, 4, 1, 43
prototropic tautomerism of, 1, 311, 339;
2, 1, 27; Suppl. 1
quaternization of, 22, 71
Heteroaromatic *N*-imines, 17, 213; 29, 71
Heteroaromatic nitro compounds, ring
synthesis of, 25, 113
Heteroaromatic radicals, Part I, general
properties; radicals with Group V ring
heteroatoms, 25, 205; Part II, radicals
with Group VI and Groups V and VI
ring heteroatoms, 27, 31
Heteroaromatic substitution, nucleophilic,
3, 285
Heterocycles
aromaticity of, 17, 255
nomenclature of, 20, 175
photochemistry of, 11, 1
by ring closure of ortho-substituted
r-anilines, 14, 211
Heterocyclic betaine derivatives of alternant
hydrocarbons, 26, 1
Heterocyclic chemistry, literature of, 7, 225;
25, 303
Heterocyclic compounds
application of Hammett equation to, 3,
209; 20, 1
(2 + 2)-cycloaddition and (2 + 2)-
cycloreversion reactions of, 21, 253
halogenation of, 7, 1
isotopic hydrogen labeling of, 15, 137
mass spectrometry of, 7, 301
quaternization of, 3, 1; 22, 71
reactions of, with carbenes, 3, 57
reactions of diazomethane with, 2, 245

N-Heterocyclic compounds
 electrolysis of, 12, 213
 reaction of acetylenecarboxylic acids and
 esters with, 1, 125; 23, 263
Heterocyclic diazo compounds, 8, 1
Heterocyclic ferrocenes, 13, 1
Heterocyclic oligomers, 15, 1
Heterocyclic pseudobases, 1, 167; 25, 1
Heterocyclic sulphur compounds, electronic
 structure of, 5, 1
Heterocyclic synthesis
 heterocyclic β -enamino esters and, 38, 299
 from nitrilium salts under acidic
 conditions, 6, 95
 through nucleophilic additions to
 acetylenic esters, 19, 279
 thioureas in, 18, 99
Hilbert-Johnson reaction of
 2,4-dialkoxypyrimidines, 8, 115
Homolytic substitution of heteroaromatic
 compounds, 16, 123
Hydantoins, chemistry of, 38, 177
Hydrogen exchange
 base-catalyzed, 16, 1
 one-step (labeling) methods, 15, 137
Hydroxamic acids, cyclic, 10, 199

I

Imidazole chemistry
 advances in, 12, 103; 27, 241
 2*H*-, 35, 375
 4*H*-, 35, 413
Indole Grignard reagents, 10, 43
Indole(s)
 acid-catalyzed polymerization, 2, 287
 and derivatives, application of NMR
 spectroscopy to, 15, 277
Indolizine chemistry, advances in, 23, 103
Indolones, isatogens and, 22, 123
Indoxazenes, 8, 277; 29, 1
Isatin, chemistry of, 18, 1
Isatogens and indolones, 22, 123
Isoic anhydrides, uses in heterocyclic
 synthesis, 28, 127
Isoindoles, 10, 113; 29, 341
Isoquinolines
 1,2-dihydro-, 14, 279

 4-oxy- and 4-keto-1,2,3,4-tetrahydro-, 15,
 99
Isothiazoles, 14, 107
 recent advances in the chemistry of
 monocyclic, 14, 1
 polycyclic, recent advances in chemistry
 of, 38, 105
Isotopic hydrogen labeling of heterocyclic
 compounds, one-step methods, 15, 137
Isoxazole chemistry, recent developments
 in, 2, 365; since 1963, 25, 147
Isoxazolidines, chemistry of, 21, 207

L

Lactim ethers, chemistry of, 12, 185
Literature of heterocyclic chemistry, 7, 225;
 25, 303

M

Mass spectrometry
 of heterocyclic compounds, 7, 301
 of nucleic acids, 39, 79
Medium-large and large π -excessive
 heteroannulenes, 23, 55
Meso-ionic compounds, 19, 1
Metallacycloalkanes, 39, 237
Metallacycloalkenes, 39, 237
Metal catalysts, action on pyridines, 2, 179
Monoazaindoles, 9, 27
Monocyclic pyrroles, oxidation, of, 15, 67
Monocyclic sulfur-containing pyrones, 8, 219
Mononuclear heterocyclic rearrangements,
 29, 141
Mononuclear isothiazoles, recent advances
 in chemistry of, 14, 1

N

Naphthalen-1,4,imines, 16, 87
Naphthyridines, 11, 124
 reactivity of, toward nitrogen
 nucleophiles, 33, 95

recent developments in chemistry of, **33**,
147

Nitriles and nitrilium salts, heterocyclic
synthesis involving, **6**, 95

Nitrogen-bridged six-membered ring
systems, **16**, 87

Nitrogen heterocycles

Conformational equilibria in saturated
six-membered rings, **36**, 1

covalent hydration in, **20**, 117

reactions of acetylenecarboxylic esters
with, **23**, 263

reduction of, with complex metal
hydrides, **6**, 45; **39**, 1

Nitrogen heterocyclic systems, Claisen
rearrangements in, **8**, 143

Nomenclature of heterocycles, **20**, 175

Nuclear magnetic resonance spectroscopy,
application to indoles, **15**, 277

Nucleic acids, mass spectrometry of, **39**, 79

Nucleophiles, reactivity of azine derivatives
with, **4**, 145

Nucleophilic additions to acetylenic esters,
synthesis of heterocycles through, **19**,
299

Nucleophilic heteroaromatic substitution, **3**,
285

O

Olefin synthesis with anils, **23**, 171

Oligomers, heterocyclic, **15**, 1

1,2,4-Oxadiazoles, **20**, 65

1,3,4-Oxadiazole chemistry, recent advances
in, **7**, 183

1,3-Oxazine derivatives, **2**, 311; **23**, 1

Oxaziridines, **2**, 83; **24**, 63

Oxazole chemistry, advances in, **17**, 99

Oxazolone chemistry
new developments in, **21**, 175
recent advances in, **4**, 75

Oxidation of monocyclic pyrroles, **15**, 67

3-Oxo-2,3-dihydrobenz[*d*]isothiazole
1,1-dioxide (saccharin) and derivatives,
15, 233

4-Oxy- and 4-keto-1,2,3,4-tetrahydro-
isoquinolines, chemistry of, **15**, 99

P

Pentazoles, **3**, 373

Peroxides, cyclic, **8**, 165 (*see also* 1,2-
Dioxetanes)

Phase transfer catalysis, applications in
heterocyclic chemistry, **36**, 175

Phenanthridine chemistry, recent
developments in, **13**, 315

Phenanthrolines, **22**, 1

Phenothiazines, chemistry of, **9**, 321

Phenoxazines, **8**, 83

Photochemistry

of heterocycles, **11**, 1

of nitrogen-containing heterocycles, **30**,
239

of oxygen- and sulfur-containing
heterocycles, **33**, 1

Physicochemical aspects of purines, **6**, 1; **24**,
215

Physicochemical properties
of azines, **5**, 69

of pyrroles, **11**, 383

3-Piperidineines, **12**, 43

Polyfluoroheteroaromatic compounds, **28**, 1

Polymerization of pyrroles and indoles,
acid-catalyzed, **2**, 1

Prototropic tautomerism of heteroaromatic
compounds, **1**, 311, 339; **2**, 1, 27;
Suppl. 1

Pseudoazulenes, **33**, 185

Pseudobases, heterocyclic, **1**, 167; **25**, 1

Purine bases, aza analogs of, **1**, 189

Purines

physicochemical aspects of, **6**, 1; **24**, 215
tautomerism, electronic aspects of, **13**, 77

Pyrans, thiopyrans, and selenopyrans, **34**, 145

Pyrazine chemistry, recent advances in, **14**,
99

Pyrazole chemistry

3*H*-, **34**, 1

4*H*-, **34**, 53

progress in, **6**, 347

Pyrazolopyridines, **36**, 343

Pyridazines, **9**, 211; **24**, 363

Pyridine(s)

action of metal catalysts on, **2**, 179

effect of substituents on substitution in, **6**,
229

- synthesis by electrochemical methods, 37, 167
1,2,3,6-tetrahydro-, 12, 43
Pyridoindoles (the carboline), 3, 79
Pyridopyrimidines, 10, 149
Pyrido[1,2-*a*]pyrimidines, chemistry of, 33, 241
Pyrimidine bases, aza analogs of, 1, 189
Pyrimidine ring, tricyclic compounds with a central, 39, 281
Pyrimidines
2,4-dialkoxy-, Hilbert-Johnson reaction of, 8, 115
tautomerism and electronic structure of biological, 18, 199
1-Pyridines, chemistry of, 15, 197
Pyrones, monocyclic sulfur-containing, 8, 219
Pyrroles
acid-catalyzed polymerization of, 2, 287
2*H*- and 3*H*-, 32, 233
oxidation of monocyclic, 15, 67
physicochemical properties of, 11, 383
Pyrrolizidine chemistry, 5, 315; 24, 247
Pyrrolizines, chemistry of, 37, 1
Pyrrolodiazines, with a bridgehead nitrogen, 21, 1
Pyrrolopyridines, 9, 27
Pyrylum salts, syntheses, 10, 241

Q

- Quaternization
of heteroaromatic compounds, 22, 71
of heterocyclic compounds, 3, 1
Quinazolines, 1, 253; 24, 1
Quinolizines, aromatic, 5, 291
Quinoxaline chemistry
developments 1963-1975, 22, 367
recent advances in, 2, 203
Quinuclidine chemistry, 11, 473

R

- Recent advances in furan chemistry, Part I, 30, 168; Part II, 31, 237
Reduction of nitrogen heterocycles with complex metal hydrides, 6, 45; 39, 1

- Reissert compounds, 9, 1; 24, 187
Ring closure of ortho-substituted *t*-anilines, for heterocycles, 14, 211
Ring synthesis of heteroaromatic nitro compounds, 25, 113

S

- Saccharin and derivatives, 15, 233
Selenazole chemistry, present state of, 2, 343
Selenium-nitrogen heterocycles, 24, 109
Selenophene chemistry, advances in, 12, 1
Selenophenes, 30, 127
Six-membered ring systems, nitrogen bridged, 16, 87
Substitution(s)
electrophilic, of five-membered rings, 13, 235
homolytic, of heteroaromatic compounds, 16, 123
nucleophilic heteroaromatic, 3, 285
in pyridines, effect of substituents, 6, 229
Sulfur compounds
electronic structure of heterocyclic, 5, 1
four-membered rings, 35, 199
Sulfur transfer reagents in heterocyclic synthesis, 30, 47
Synthesis, of tetracyclic and pentacyclic condensed thiophene systems, 32, 127
Synthesis and reactions of 1-azirines, 13, 45
Synthesis of heterocycles
heterocyclic β -enamino esters as synthons in, 38, 299
from nitrilium salts under acidic conditions, 6, 95
through nucleophilic additions to acetylenic esters, 19, 279
thioureas in, 18, 99

T

- Tautomerism
electronic aspects of purine, 13, 77
and electronic structure of biological pyrimidines, 18, 199
prototropic, of heteroaromatic compounds, 1, 311, 339; 2, 1, 27; Suppl. 1

- Tellurophene and related compounds, **21**, 119
1,2,3,4-Tetrahydroisoquinolines, 4-oxy- and 4-keto-, **15**, 99
1,2,3,6-Tetrahydropyridines, **12**, 43
Tetrazole chemistry, recent advances in, **21**, 323
Theoretical studies of physicochemical properties and reactivity of azines, **5**, 69
1,2,4-Thiadiazoles, **5**, 119; **32**, 285
1,2,5-Thiadiazoles, chemistry of, **9**, 107
1,3,4-Thiadiazoles, recent advances in the chemistry of, **9**, 165
Thiathiophthenes
 (1,6,6a S^{IV} -trithiapentalenes), **13**, 161
1,2,3,4-Thiatrazoles, **3**, 263; **20**, 145
1,4-Thiazines and their dihydro derivatives, **24**, 293
4-Thiazolidinones, **25**, 8
Thienopyridines, **21**, 65
Thienothiophenes and related systems, chemistry of, **19**, 123
Thiochromanones and related compounds, **18**, 59
Thiocoumarins, **26**, 115
Thiophenes, chemistry of, recent advances in, **1**, 1
Thiopyrones (monocyclic sulfur-containing pyrones), **8**, 219
Thioureas in synthesis of heterocycles, **18**, 99
Three-membered rings with two heteroatoms, **2**, 83; **24**, 63
Transition organometallic compounds in heterocyclic synthesis, use of, **30**, 321
1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes, **10**, 149
1,2,3-Triazines, **19**, 215
1,2,3-Triazoles, **16**, 33
 Δ^2 -1,2,3-Triazolines, **37**, 217
 Δ^3 - and Δ^4 -1,2,3-Triazolines, **37**, 351
Triazolopyridines, **34**, 79
1,2,3-Triazolo[4,5-*d*]pyrimidines (8-azapurines) chemistry of, **39**, 117
Tricyclic compounds, with a central pyrimidine ring and one bridgehead nitrogen, **39**, 281
1,6,5a S^{IV} -Trithiapentalenes, **13**, 161

This Page Intentionally Left Blank